

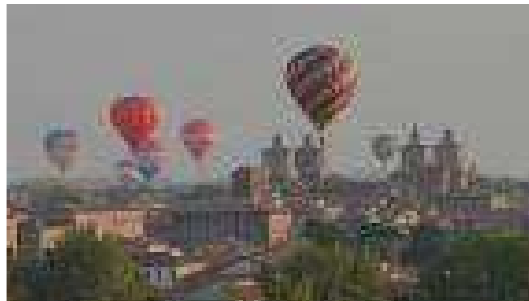


Società Medico Chirurgica di Ferrara

Ferrara, 19 maggio 2012

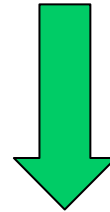
LE MANIFESTAZIONI CUTANEE delle MALATTIE AUTOINFIAMMATORIE

Vincenzo Bettoli





SINDROMI AUTOINFIAMMATORIE



- Definizione relativamente recente (1999 Kastner, O'Shea)
- Rare
- Aspetti dermatologici:
 - frequentemente presenti
 - raramente preminenti
 - in alcuni casi caratterizzano il quadro clinico
(es. PAPA syndrome, SAPHO, ecc...)



Table 2: Skin manifestations in autoinflammatory diseases.

Disease	Cutaneous manifestations	Frequency
Familial Mediterranean fever (FMF)	Erysipelas-like erythemas, Henoch-Schönlein purpura, palmoplantar erythemas, Raynaud-like phenomena	12–43 %
TNF receptor-associated periodic syndrome (TRAPS)	Round-oval, annular, gyrated erythemas and urticarial plaques wandering from proximal to distal, <i>often with</i> underlying myalgias	80 %
Hyperimmunoglobulinemia D syndrome (HIDS)	Morbilliform > urticarial exanthema, oral and genital aphthous ulcerations, purpura, erythema nodosum	< 70 %
CAPS	Painful, non-pruritic, maculopapular, not entirely urticaria-typical exanthemas	100 %
PAPA syndrome	Disseminated pyoderma gangrenosum, cystic acne	100 %
Schnitzler syndrome	Non-pruritic, wandering urticaria-like exanthemas	100 %
PFAPA syndrome	Aphthous stomatitis, more rarely exanthemas with predilection for the trunk	100 %
Adult Still disease	Fleeting maculopapular, salmon-color exanthema	< 100 %
Deficiency of IL-1 receptor antagonist (DIRA)	Localized or generalized pustulosis similar to pustular psoriasis, occasionally pyoderma gangrenosum	< 100 %
SAPHO syndrome	Palmoplantar pustulosis, acne	100 %
Behçet disease	Bipolar aphthae, erythema nodosum	100 %
Gout	Podagra, gout tophi	
Blau syndrome	Clinically small papules, histologically sarcoidal dermatitis	< 100 %



Familial Med Fever (FMF)	Usually before 20	Fever, sierositis Skin: 12-43% - unspecific purpuriform exantemas, erysipelas-like erythema (feet)
TNF-R1 associated fever syn. (TRAPS)	After infancy - before 20	Fever, sierositis Skin: 80% > erythemas, urticarial plaques, limbs near the trunk expand distally
HyperIgD Syndrom (HIDS)	Start 1° y	Fever, syst symptoms. Skin: 2/3 - maculo-papular morbilliform urticarial exantem, erythema nodosum 50% aphthae (d.d. Behcet) Trigg: vaxine, emotional physical stress
CAPS (cryopirin-assoc fever synd) 1) Fam Cold Urtic 2) Muckle-Wells 3) CINCA	Start 1° m " "	Skin 100% Fever. Skin: maculopapular non pruritic " " (severe). Maculopapular, urtic-like no pruritus
PAPA	Chilhood (arthritis) Puberty (acne)	Pyogenic aseptic arthritis, Pyoderma gangrenosum, acne (100%)



Schnitzler syndrom	Mild-childhood	Skin 100%: non pruritic urticaria-like exanthemas
Periodic Fever Aphthae Pharyngitis (PFAPA)	Before 5	Fever. Skin: frequent aphthae 100% (d.d. Behcet) rare exanthemas
Adult-onset Still syndrome	Adults under 35	Fever, arthritis. Skin: fleeting macular to maculopapular salmon coloured exanthema (<100%)
Deficiency of IL-1 receptor antagonist (DIRA)	1° week	Osteomyelitis, periostitis. Skin: grouped or generalized pustular exanthemas (d.d. pustular psoriasis)
SAPHO	adulthood	Palmoplantar pustulosis, acne

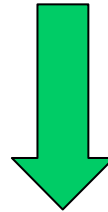


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ACNE



PAPA syndrome

(Pyogenic Arthritis Pyoderma gangrenosum Acne)



d.d. dell'acne

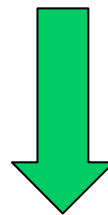


20th European Academy of Dermatology and Venereology Congress
Lisbon, October 20-24th, 2011

Thomas Ruzicka: **PASH syndrome - a new clinical entity ?**

Journal of the American Academy of Dermatology 2012;66:409
Braun-Falco M, et al.

**Pyoderma gangrenosum, Acne, and Suppurative Hidradenitis (PASH)
a new autoinflammatory syndrome distinct from PAPA syndrome**



ACNE e

IDROSADENITE SUPPURATIVA - ACNE INVERSA



Braun-Falco M, et al. JAAD 2012;66:409
Pyoderma gangrenosum, Acne, and Suppurative Hidradenitis (PASH)
a new autoinflammatory syndrome distinct from PAPA syndrome



	Patient 1	Patient 2
Age/sex/descent	34 - M - Russian	44 - M - German
Severe Acne	Yes - from adolescence	Yes - at 17-18 yrs
Acne Inversa - Suppur. Hidraden	Yes - for 7 yrs	Yes - axillae, groin
Pyod. Gangrenos	Yes - for 6 months	Yes - for 1 year
Pyogenic Arthritis	No	No
Serum amyloid A	slight increase (22 mg/L)	elevated (66.2 mg/L)
<i>PSTPIP1, MEFV</i> <i>NLRP3, TNFRSF1A</i> Lenght poly-CCTG	no mutations " increased: 5r/8r (n. 5r)	no mutation " increased: 5r/6r (n. 5r)
Therapy	O.Isotr, Anakinra, Cya	Pred, AZA, top tacrolim



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Pyoderma gangrenosum, Acne, and Suppurative Hidradenitis (PASH)
a new autoinflammatory syndrome distinct from PAPA syndrome



	PAPA syndrome	PASH syndrome
Severe Acne	Yes	Yes
Acne Inversa - Suppur. Hidraden	No	Yes
Pyod. Gangrenos	Yes	Yes
Pyogenic Arthritis	Yes	No
<i>PSTPIP1</i> , Length poly-CCTG (in <i>PSTPIP1</i> promoter region)	Mutation n.n.	No mutation increased: 8r/6r (n. 5r)* *As in aseptic abscesses syndrome

* Predisposition to inflammatory reactions dominated by PMN and monocytes



ACNE INVERSA HIDRADENITIS SUPPURATIVA

"HS is a chronic, inflammatory, recurrent, debilitating, skin follicular disease that usually presents after puberty with painful deep seated, inflammed lesions in the apocrine gland-bearing area of the body, most commonly, the axillary, inguinal and anogenital regions"



*HS Foundation - 2° Meeting
San Francisco March 2009*



ACNE INVERSA HIDRADENITIS SUPPURATIVA

Point prevalence at 1 year of **1%**
Females / males 3:1



Most commonly affected area is **axilla**. Genitofemoral area for females.

Most commonly **develops in the 20s**

Prevalence declines over 50 yrs

Negative effects on QoL



ACNE INVERSA *HIDRADENITIS SUPPURATIVA*

Clinical associations:

severe acne, pilonidal cysts, dissecting cellulitis of scalp
(Plewig 1989)

50% increase in risk of cancer of any kind

↑ frequency: **squamous-cell carcinoma of the buttocks**

↑ frequency in **Chron's patients**

Arthritis is also more frequent





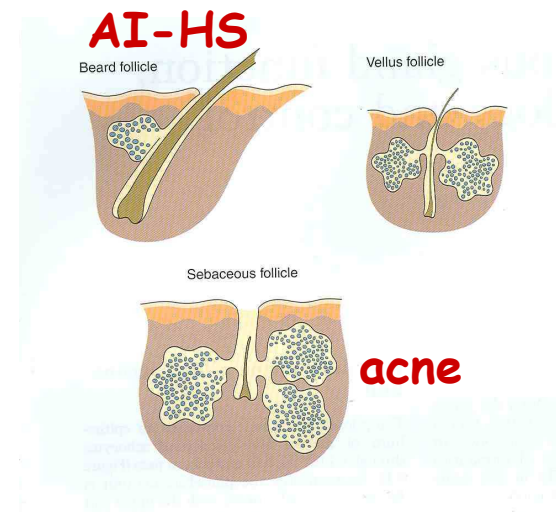
ACNE INVERSA HIDRADENITIS SUPPURATIVA

ETIOPATHOGENESIS: **unknown** !
It is likely **multifactorial**

- Long thought to be a disorder
of apocrine origin

- It is now thought to be **caused**
by **follicular occlusion**:

- 1) **hyperkeratinization** of follicular
infundibulum
- 2) **follicular occlusion**
- 3) **rupture** of dilated follicles
- 4) **inflammation**





ACNE INVERSA HIDRADENITIS SUPPURATIVA

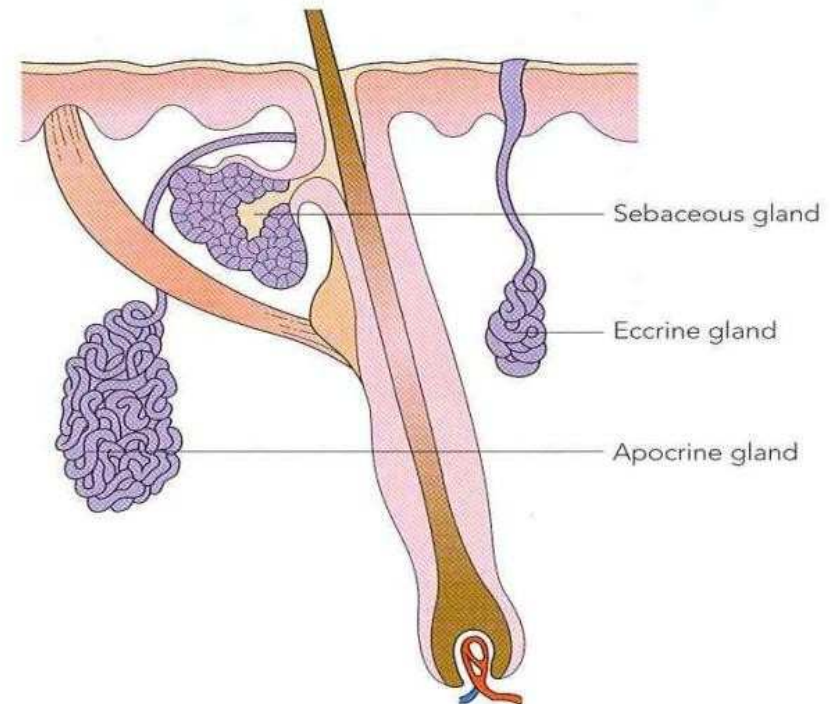
ETIOPATHOGENESIS: **genetic predisposition**

Positive family history 35-40%

Pattern of transmission
consistent with **autosomal
dominant inheritance**

Mutation of γ -secretases
(Chinese and French families)
transmembrane enzymatic
complexes (... , nicastrin, ...)

**Catalyze cleavage of a wide range
of transmembrane proteins**
(including B-amyloid)





ACNE INVERSA *HIDRADENITIS SUPPURATIVA*

ETIOPATHOGENESIS: **exogenous factors**

Sigarette smoking

Obesity

Trauma, friction

Hormonal influences (?)

Biofilm (Staf, Strept)





ACNE INVERSA HIDRADENITIS SUPPURATIVA



ETIOPATHOGENESIS

Significantly elevated secretion
of cytokines including:

IL-1B, CXCL9, MIG (monokine
Induced by IFN- γ), IL-10, IL-11,
IL-17A, TNF α
(van der See et al ...)

Abundantly expressed by
macrophages in the dermis:

IL-12, IL-23, IL-17 producing
T helper cells (Th17)

Altered innate immune response
to commensal microbiota

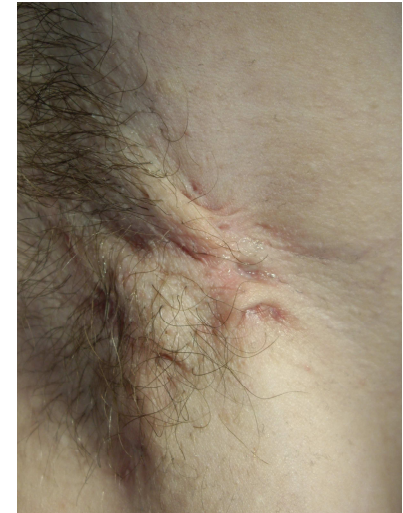




ACNE INVERSA HIDRADENITIS SUPPURATIVA

Hurley's staging is **simple** and relies on the **subjective extent of diseased tissue**

- I) **Abscess** formation (single or multiple) without **sinus tract** and **cicatrization**
- II) One or more widely separated recurrent **abscesses** with **tract formation** and **scars**
- III) **Multiple interconnected tracts** and **abscesses** throughout an **entire area**



Hurley HJ. In Roenick RK et al eds. Dermatologic surgery. M.Dekker. NY, 1989



ACNE INVERSA - IDRADENITIS SUPPURATIVA staging HSSI

Table I. Hidradenitis Suppurativa Severity Index

Score/category	No. of sites	Body surface area (%) [*]	No. of lesions (erythematous, painful)	Drainage (No. of dressing changes/working/leisure h) [†]	Pain (VAS)
0	0	0	0	0	0-1
1	1	1	1-2		
2	2	2-3	2-3	1	2-4
3	3	4-5	4-5	>1	5-7
4	≥4	>5	>5		8-10

Composite score of symptoms and signs ranging from 0 to 19
(mild 0-7, moderate 8-12, severe > 13)

Grant A., et al. JAAD 2010;62:205-17





HS: treatment options

Medical Therapy

- Antibiotics
topical, systemic
- Dapsone
- Antiandrogens
- Corticosteroids
intralesional, systemic
- Retinoids
- Zinc
- Anti-TNF α
- Cya
- anti IL-1

Surgery

- Drainage
- Local excision
- Radical excision

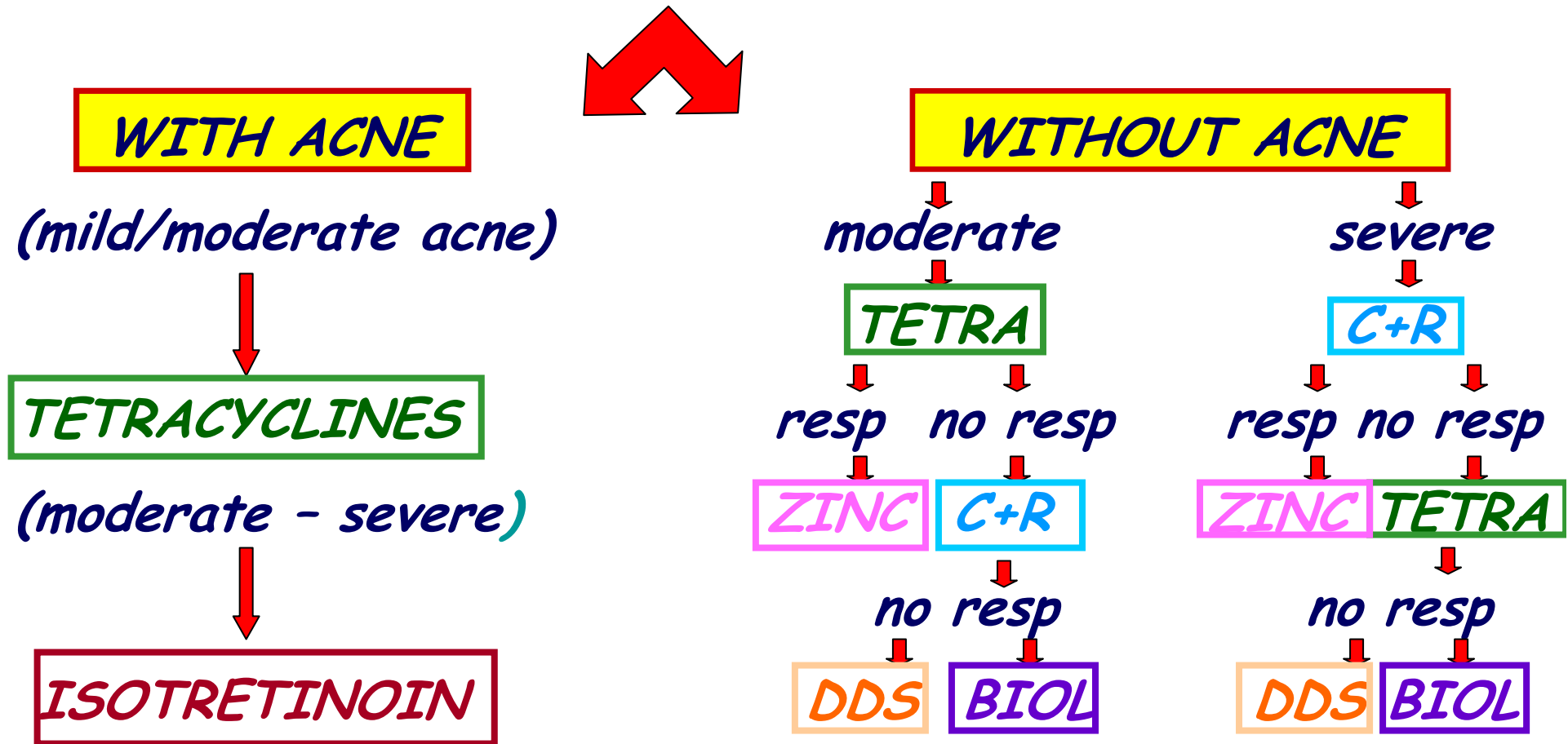
Miscellanea

- Botulinum toxin
- Cryosurgery
- Radiotherapy
- Laser
- Radiofrequency
- PDT



HIDRADENITIS SUPPURATIVA / ACNE INVERSA

(MEDICAL THERAPY - ALGORYTHM - proposal)





ACNE INVERSA HIDRADENITIS SUPPURATIVA

No uniformly effective
single therapy

Array of different treatment
modalities

Dermatologist experience

Wide surgical excision
provide best QoL (finally)





***DIPARTIMENTO MEDICINA CLINICA e SPERIMENTALE
UNIVERSITA' DI FERRARA
SEZIONE DERMATOLOGIA - AMBULATORIO ACNE***



PROGETTO GISED



***REGISTRO ITALIANO
IDROSADENITE SUPPURATIVA - ACNE INVERSA***



REGISTRO ITALIANO IDROSADENITE SUPPURATIVA - ACNE INVERSA

IN COSA CONSISTE - OBIETTIVI

- 1) REGISTRO NAZIONALE PAZIENTI-DATABASE**
- 2) IMPLEMENTAZIONE CONOSCENZA ED ESPERIENZA CLINICA**
- 3) PROMUOVE INFORMAZIONE SULLA HS-AI**
- 4) ESECUZIONE STUDI CLINICI - EPIDEMIOLOGICI - RICERCA APPLICATA**



www.inversaonlus.com



CONCLUSIONI

- **Quadri cutanei associati alle Sindromi Autoinfiammatorie**
frequenti
aspecifici: esantemi, orticaria-like
specifici: afte, acne, pioderma gangrenoso
raramente predominanti
- **Acne Inversa - Idrosadenite Suppurativa**
inclusione nella lista delle Sindromi
Autoinfiammatorie necessita di conferma



Dipartimento di Medicina Clinica e Sperimentale – Sezione di Dermatologia
Università degli Studi di Ferrara





Ambulatorio dedicato

**ACNE INVERSA
IDROSADENITE SUPPURATIVA**



ACNE FERRARA 2012

Ac - Fe

**10° Meeting di Aggiornamento su
Acne e Dermatosisi Correlate**

Ferrara 5-6 ottobre 2012



Ambulatorio Acne Ferrara 1997 - 2012



15° Anniversario

Ac - Fe