Patología cutánea en el paciente sometido a agentes citostáticos

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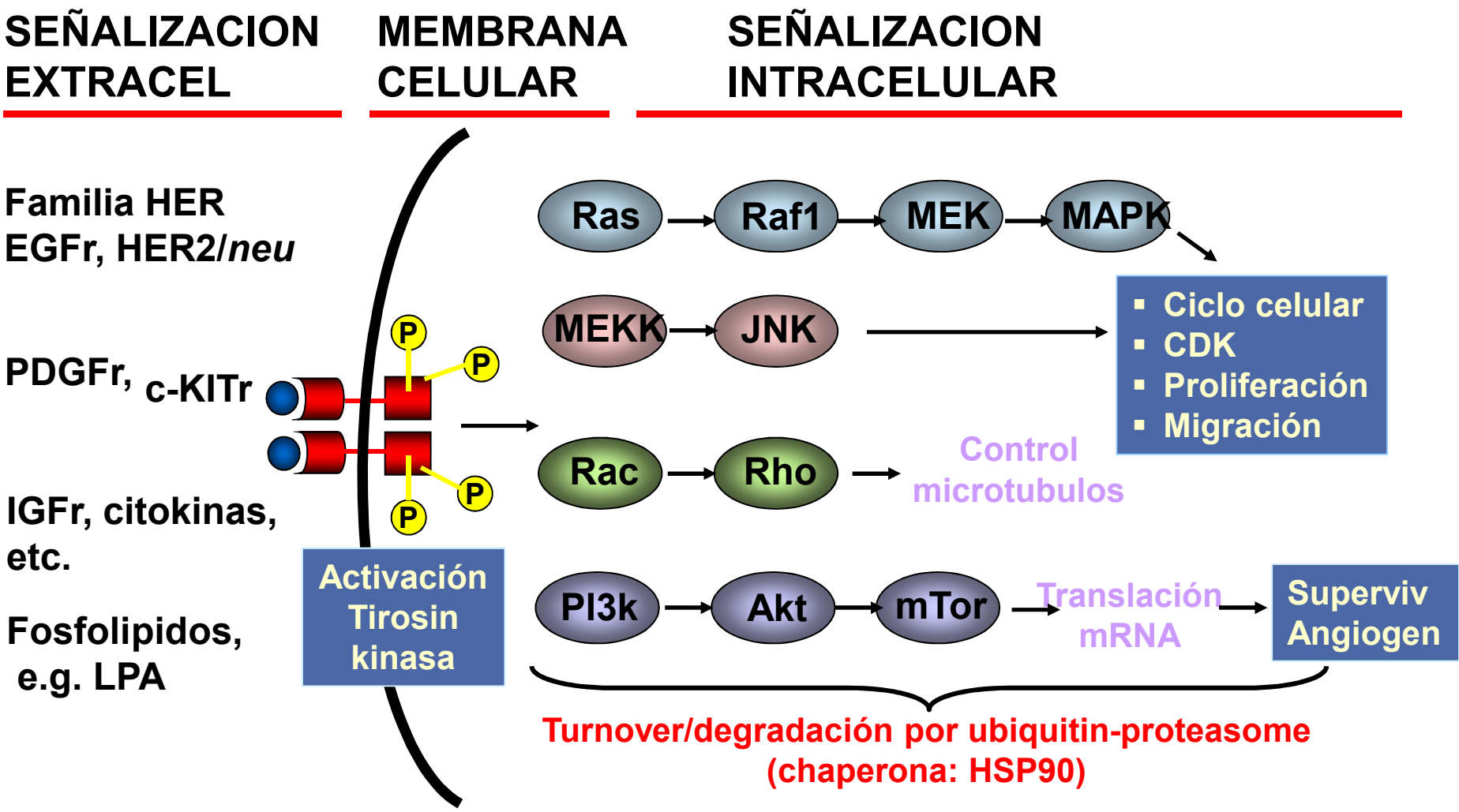
EFECTOS ADVERSOS CUTÁNEOS DE LA QUIMIOTERAPIA ANTINEOPLASICA

- CITOSTÁTICOS CLÁSICOS
  - Daño frente a células con alta capacidad de replicación
  - Patrones de reacción comunes a diferentes agentes
  - Reacciones tóxicas similares a la toxicidad medular o digestiva
  - Dosis dependiente
  - Lesiones cutáneas ocasionalmente toxicidad limitante de dosis
- AGENTES FRENTE A DIANAS MOLECULARES
  - Daño frente a vias de señalización
  - Patrones de reacción dependientes de la diana bloqueada
  - No siempre dosis dependiente
  - Lesiones cutáneas frecuentemente toxicidad limitante de dosis

NUEVOS TRATAMIENTOS ANTINEOPLASICOS



Incidencia de lesiones cutáneas en el paciente sometido a QT convencional

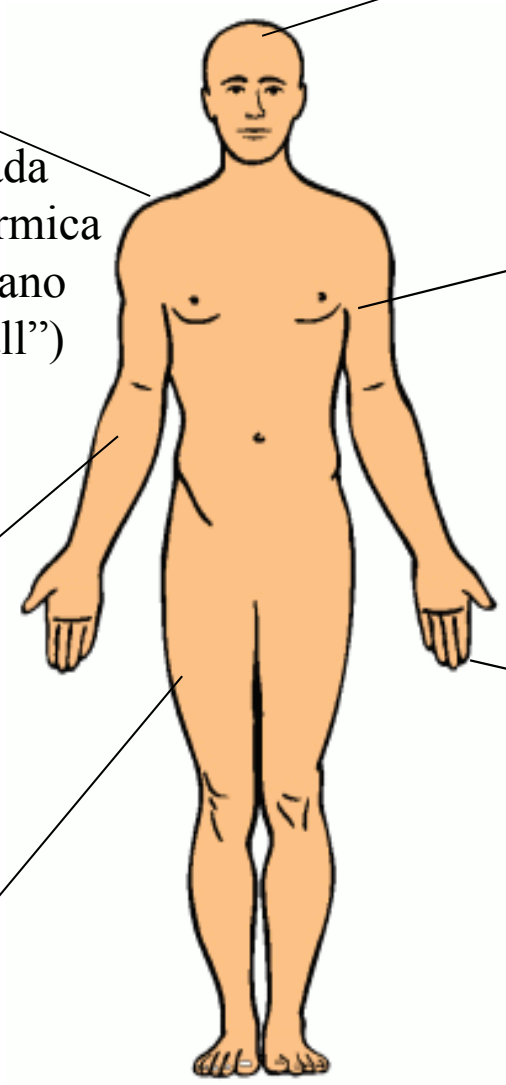
	Fariña MC Acta DS 2001	Sanmartin O JEADV 2003
Nº pacientes oncológicos incluidos	600	2186
Incidencia de lesiones cutáneas	28'9%	23'14% (506/2186)
Incidencia metástasis cutáneas	4'5%	2'29%
Infecciones cutáneas	4'6%	3'8%
Síndromes paraneoplásicos	6%	2'1%
Reactivación de dermatosis previas	2%	1'78%
Toxicodermias por otros fcos,	--	1'1%
Lesiones cutáneas inducidas por QT	10'11%	12'07% (264/2186)

Fariña MC.: Manifestaciones cutáneas en el paciente onco-hematológico. U.Autónoma Madrid. 2001. Fundación Jiménez-Díaz
Sanmartin O.: Cutaneous side effects of antineoplastic agents. JEADV 2003; 17 (Suppl. 3): 3-55

Lesiones cutáneas inducidas por QT convencional

- Incidencia de lesiones cutáneas atribuibles al tratamiento citostático (10-12% pacientes)
- Los agentes citostáticos pueden producir lesiones cutáneas por dos mecanismos:
  - Como cualquier otro fármaco, reacciones de hipersensibilidad. Solo 1 de cada 6
  - En base a su capacidad citotóxica dañando células diana en epidermis y anejos cutáneos con elevada tasa mitótica. 5 de cada 6

LESIONES CUTANEAS INDUCIDAS POR CITOTOXICIDAD



PELO:
alopecia
foliculitis

EPIDERMIS:
Necrolisis epidérmica localizada
Síndrome de citotoxicidad epidérmica
Eritema acral/ Síndrome pie-mano
Reacciones reactivación (“recall”)

GLANDULAS SUDORALES
Hidradenitis neutrofílica
Siringometaplasia escamosa ecrina

TEJIDO SUBCUTANEO:
Extravasacion

UÑAS:
onicodistrofia
onicolisis
onicomadesis

MELANOCITOS
Hiperpigmentacion

COMMENTARY

Toxic erythema of chemotherapy: A useful clinical term

Jean L. Bolognia, MD,[a] Dennis L. Cooper, MD,[b] and Earl J. Glusac, MD[a,c]
New Haven, Connecticut

J Am Acad Dermatol 2008
Volume 59, Number 3

- ERITEMA TOXICO DE LA QT
- Término propuesto por J Bolognia
- Unifica diferentes entidades descritas en la literatura y que cursan con daño epidérmico y ecrino
- Permite comunicación con el oncólogo
- Pretende reflejar la naturaleza no alergica y no infecciosa de una erupción cutánea durante la QT

Table II. Entities within the spectrum of toxic erythema of chemotherapy[2,3,18-28]

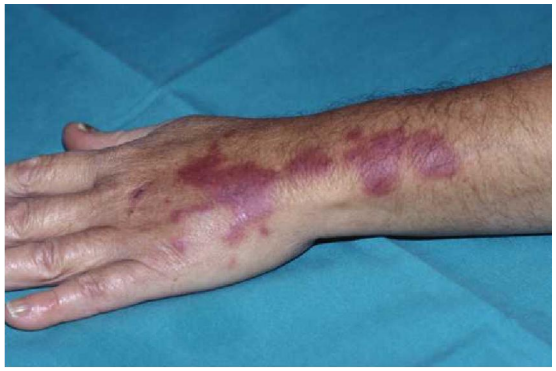
AraC (cytarabine) ears
Burgdorf's reaction
Chemotherapy-associated eccrine reactions
Eccrine squamous syringometaplasia, chemotherapy-induced
Epidermal dysmaturation, chemotherapy-induced
Epidermal dystrophy (secondary to cytotoxic agents*)
Erythrodysesthesia
Acral erythema
Acral erythrodysesthesia
Chemotherapy-induced acral erythema (CIAE or CAE)
Hand–foot syndrome
Palmar–plantar erythema
Palmar–plantar (palmoplantar) erythrodysesthesia
Toxic acral erythema
Toxic erythema of the palms and soles
Intertriginous eruption associated with chemotherapy
Intertrigo-like eruption, chemotherapy-induced
Flexural erythematous eruption (following autologous PBSCT)
Intertrigo dermatitis
Neutrophilic eccrine hidradenitis, chemotherapy-associated
Chemotherapy-induced hidradenitis
Drug-induced hidradenitis

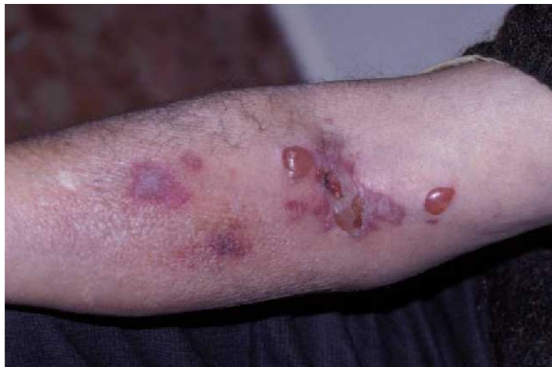
Eritema tóxico de la quimioterapia convencional

- Lesiones en la zona de inyección
- Erupciones difusas epidérmicas
- Erupciones en pliegues (afectacion sudoral)
- Reacciones de reactivación (recall)
- Eritema acral inducido por la quimioterpia

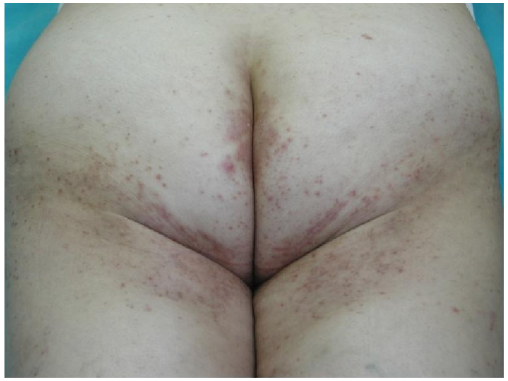
Afectación epidérmica por QT convencional

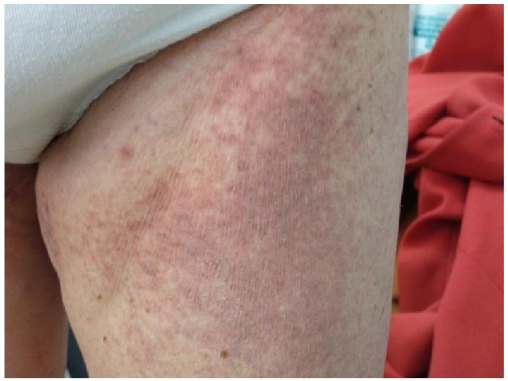
Necrolisis epidérmica en el punto de inyección



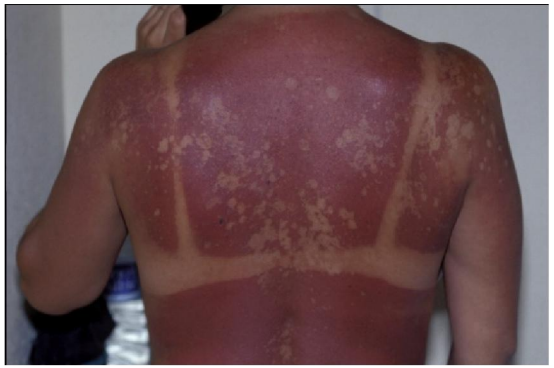


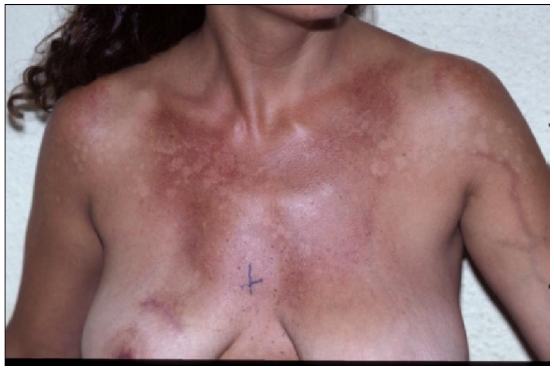
Erupciones difusas

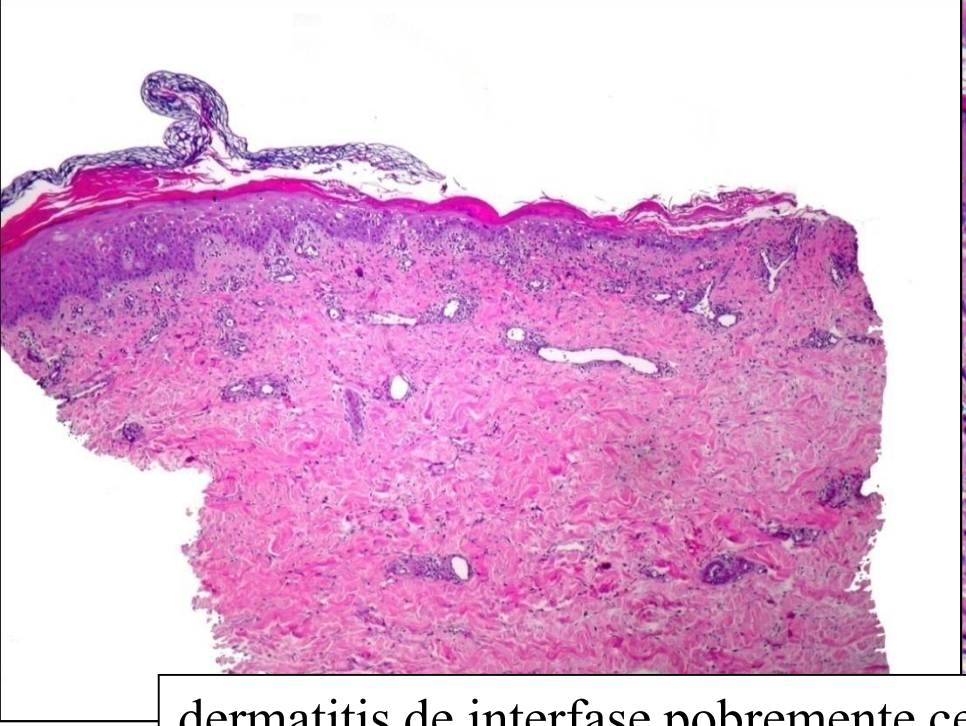


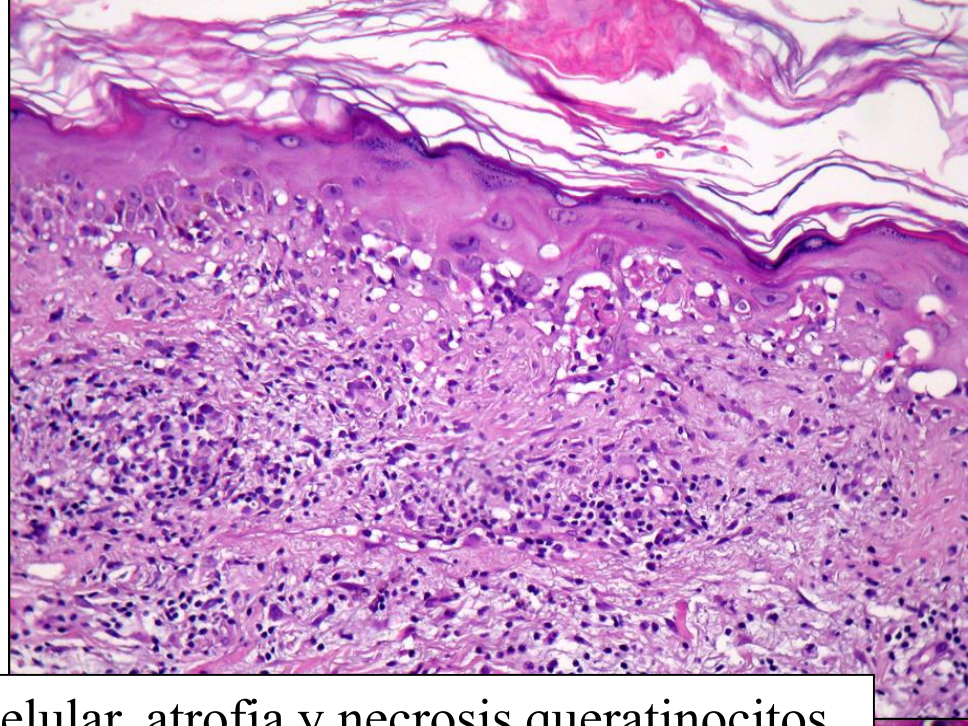


Reacciones recall

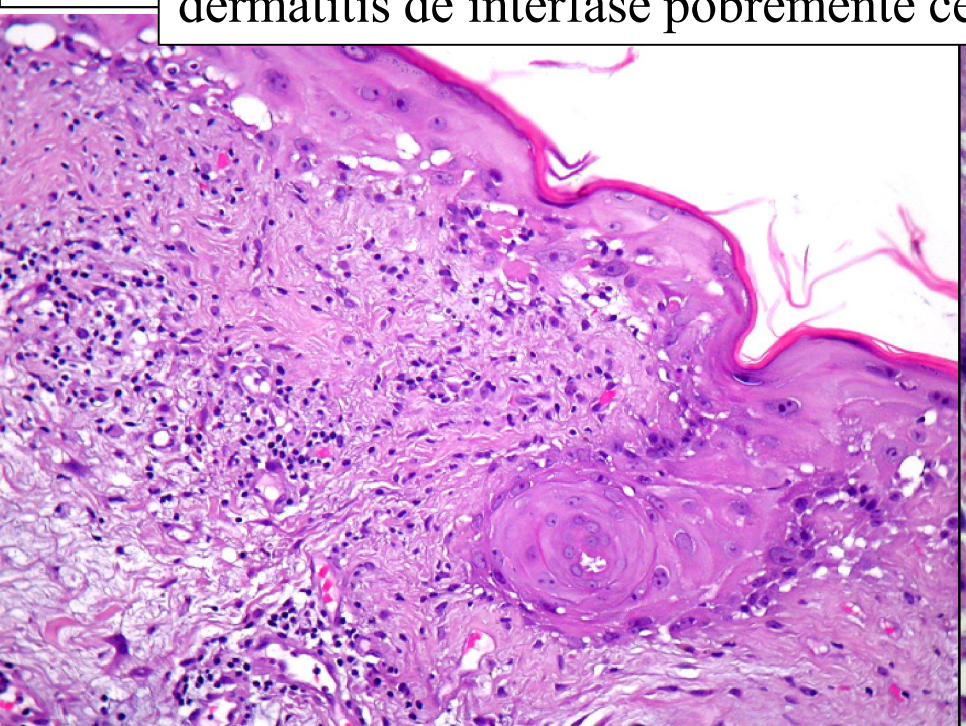


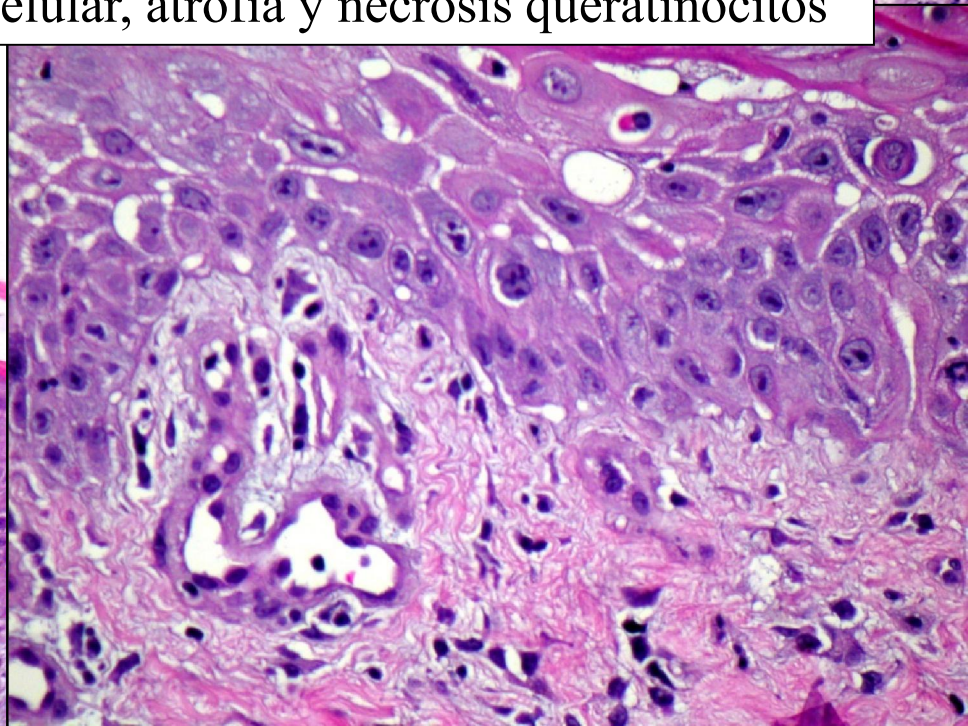


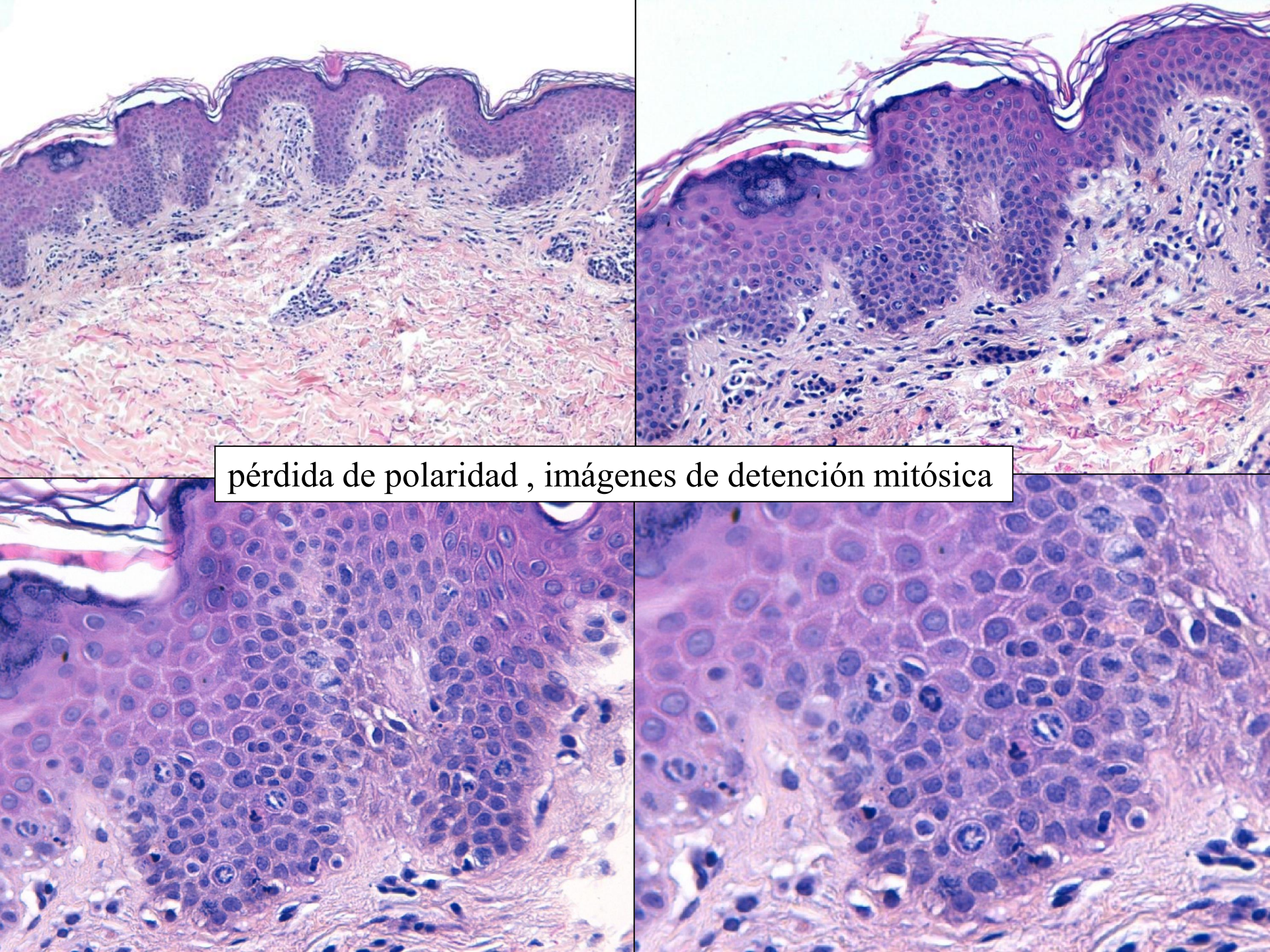




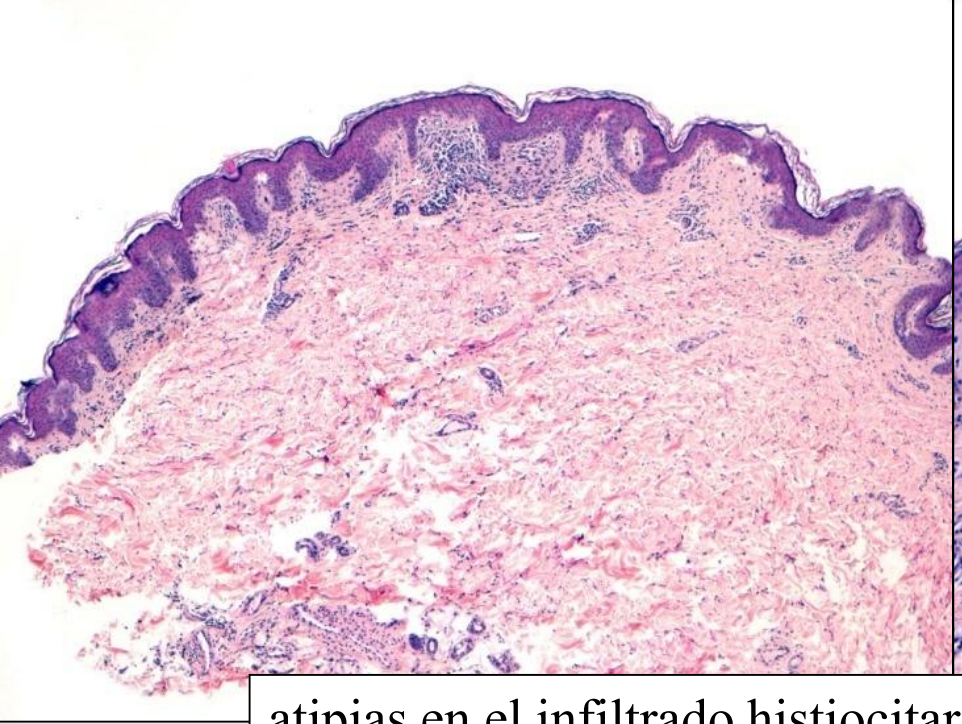
dermatitis de interfase pobremente celular, atrofia y necrosis queratinocitos

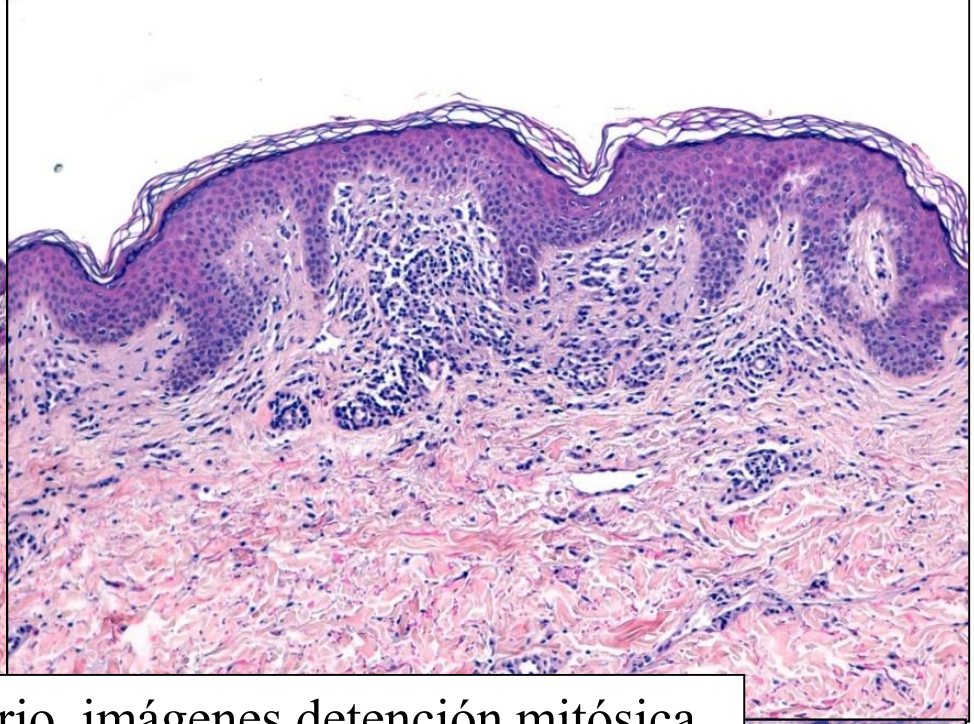




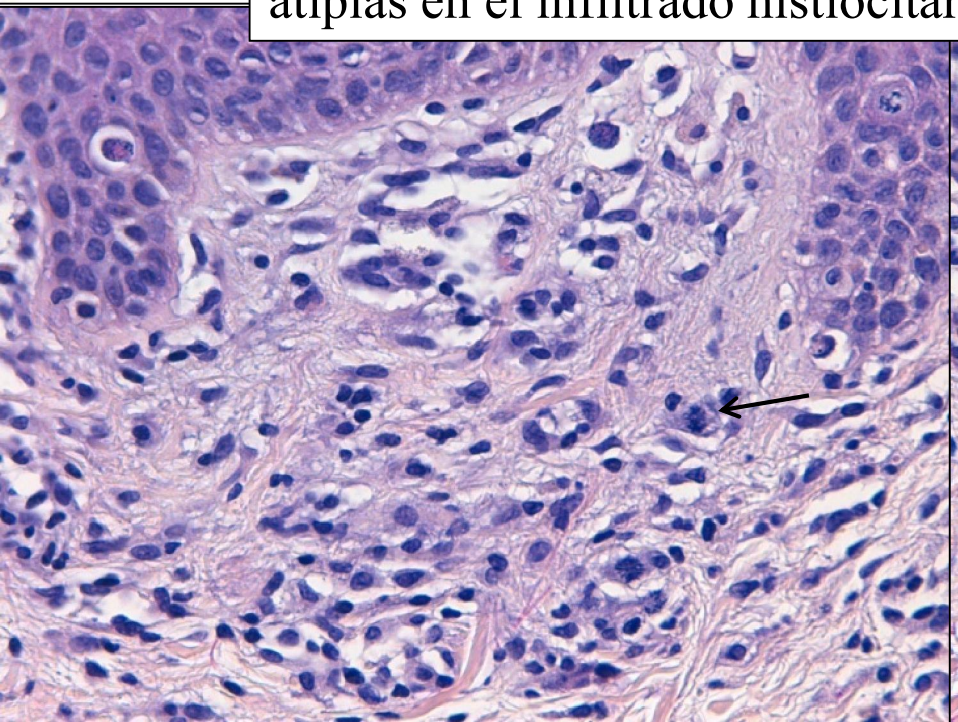


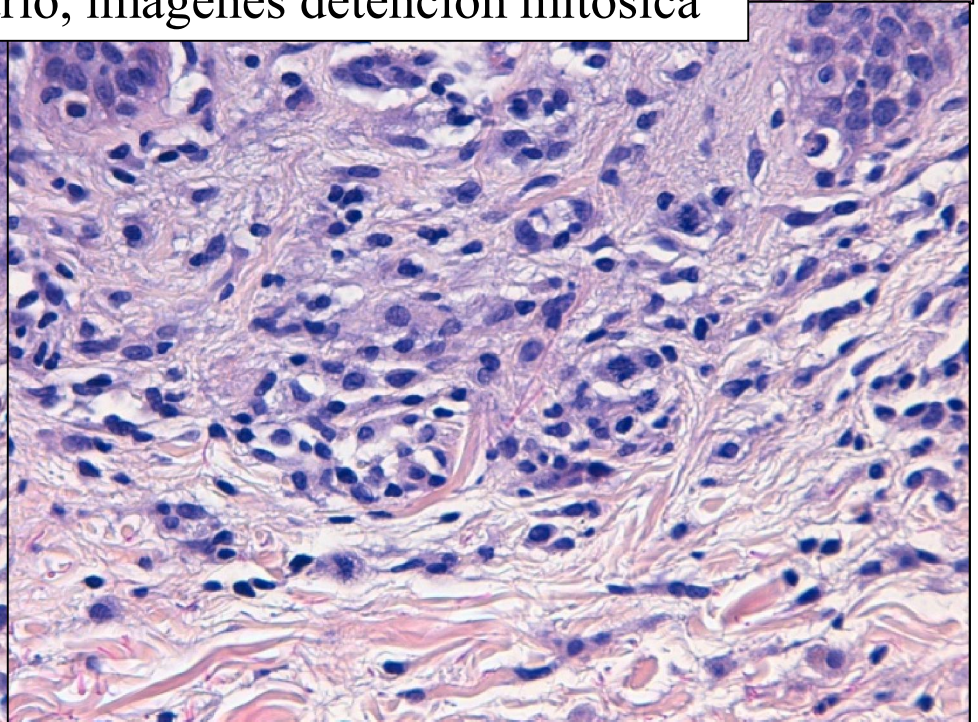
pérdida de polaridad , imágenes de detención mitósica





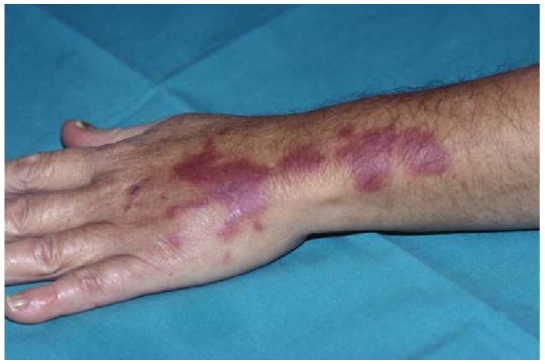
atipias en el infiltrado histiocitario, imágenes detención mitósica

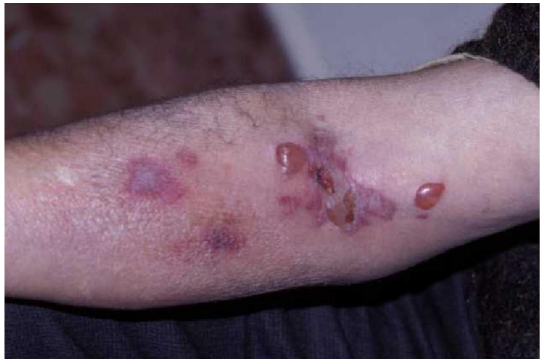




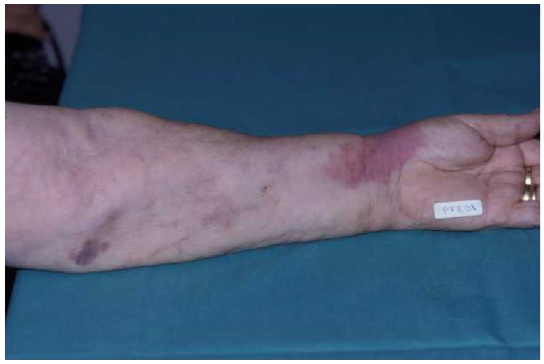
Necrolisis epidérmica localizada en el punto de inyección

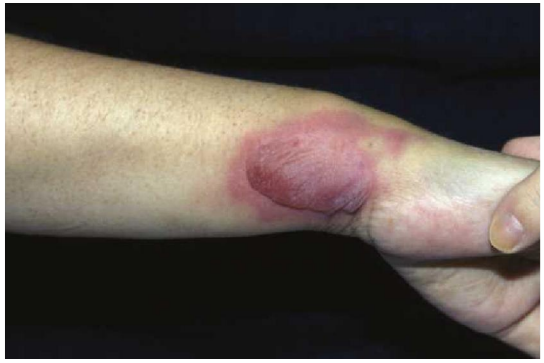
Eritema multiforme-like



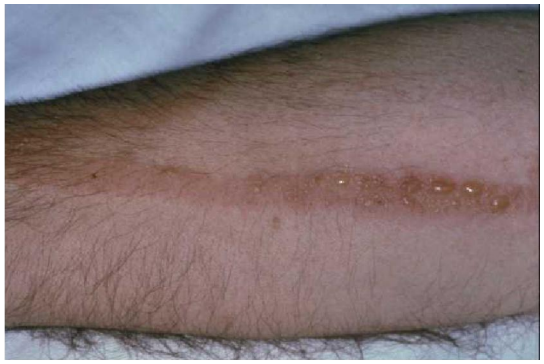


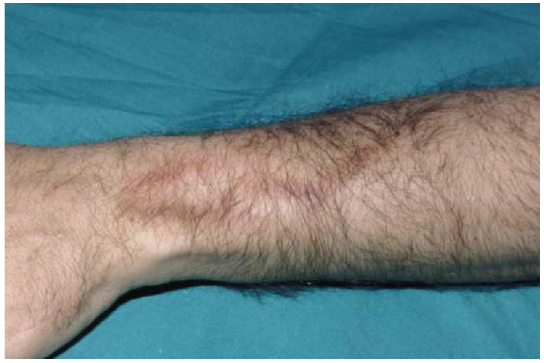
Erupción fija por fármacos-like





Erupción suprav. persistente



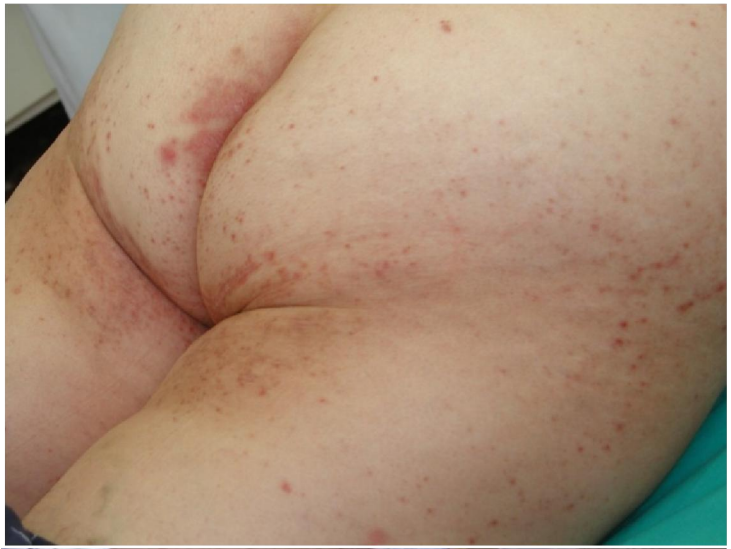


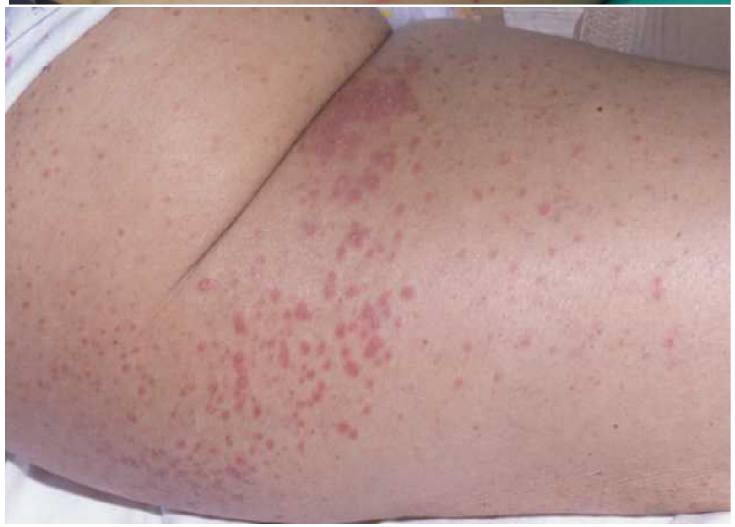
Taxanos. Vinorelbina. 5 FU

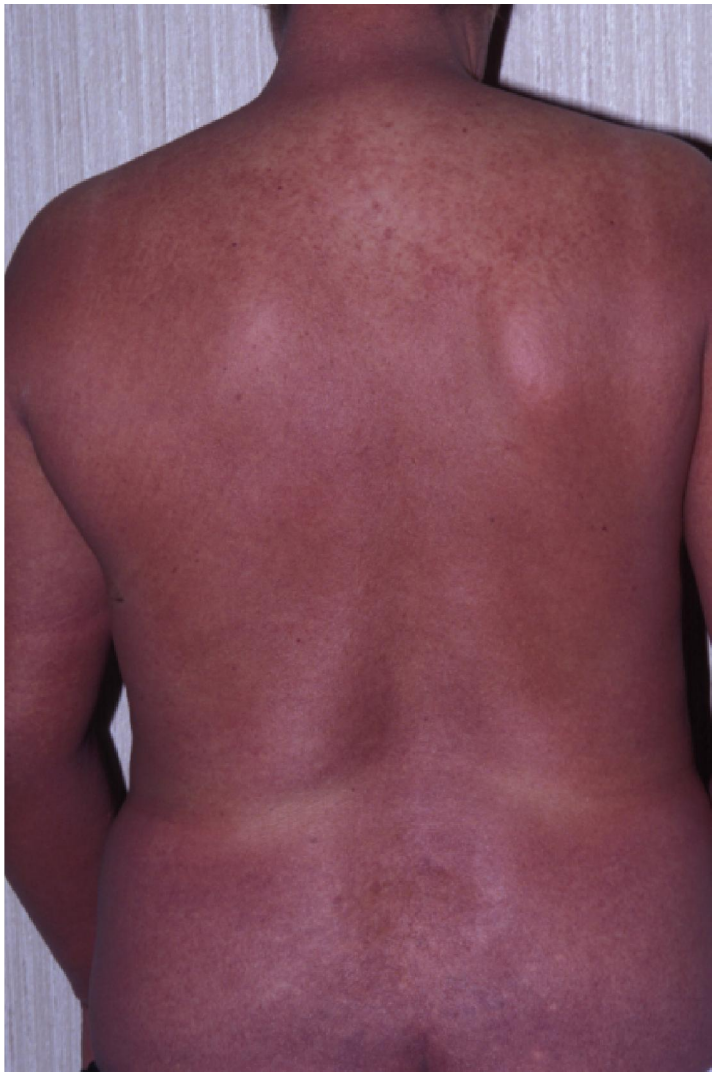
CTCAE 4.03, june 2010
Skin and subcutaneous tissue disorders

- Alopecia
- Body odor
- Bullous dermatitis
- Dry skin
- Erythema multiforme
- Erythroderma
- Fat atrophy
- Hirsutism
- Hiperhidrosis
- Hipertricosis
- Hipohidrosis
- Lipohypertrophy
- Nail discoloration
- Nail loss
- Nail ridging
- Pain of skin
- Palmar-plantar erythrodysesthesia syndrome
- Periorbital edema
- Photosensitivity
- Pruritus
- Purpura
- Rash acneiform
- Rash maculo-papular
- Skin hyperpigmentation
- Skin hypopigmentation
- **Injection site reaction**
- **Infusion site extravasation**

Eritema tóxico por QT

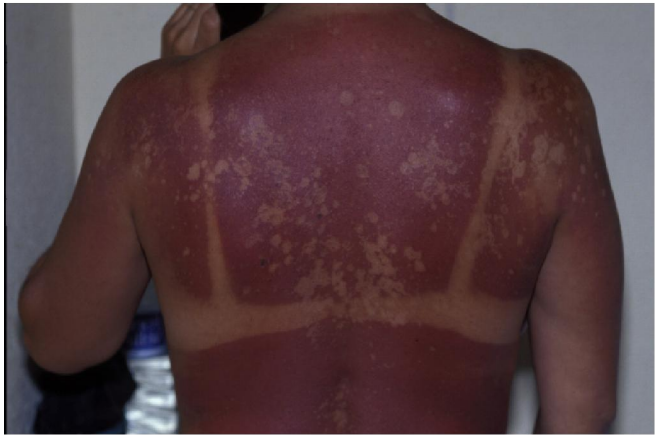


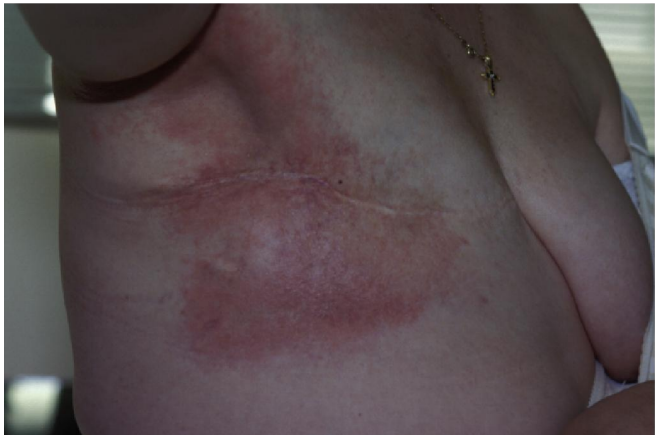


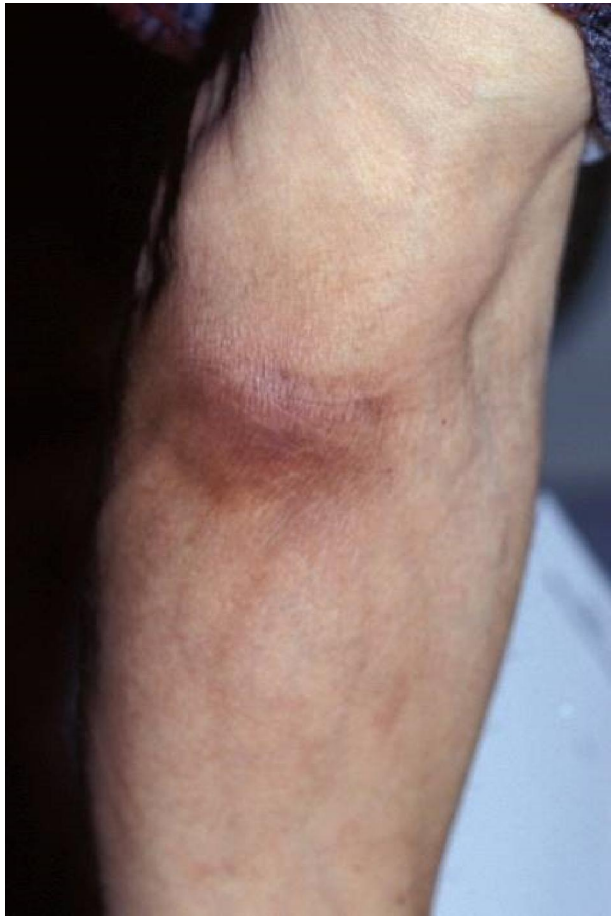


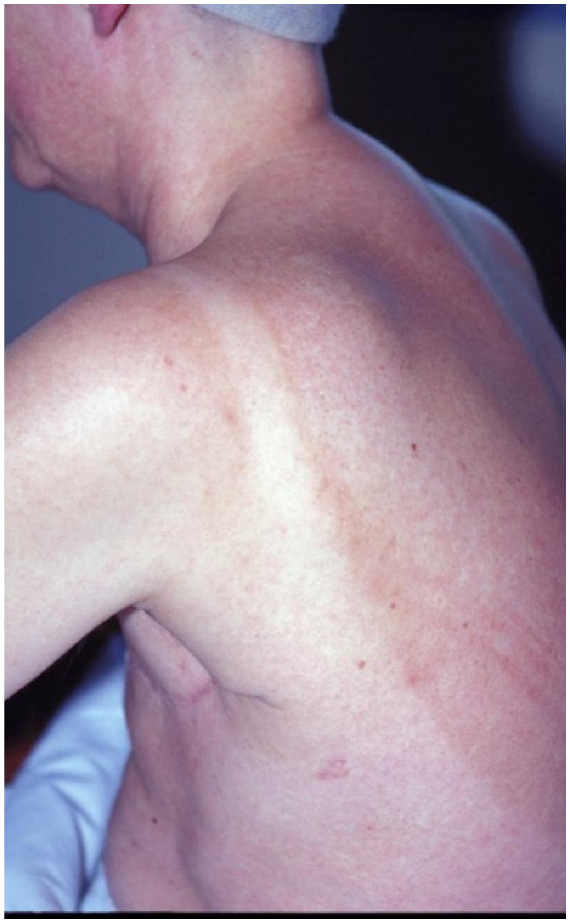
TAMO, DOXORUBICINA-L y TAXANOS

Reacciones de “recall”









Taxanos, MTX, CFM

Dermatitis bilateral con SMEE inducida por quimioterapia

- Inicio entre las 24-48 horas tras tto
- En ciclos iniciales (1º-2º)
- Erupción eritemato-edematosa, ocasionalmente vesiculosa
- En axilas, ingles, cuello, submamaria, párpados
- Histológicamente cursa con SMEE

Chemotherapy-related bilateral dermatitis associated with eccrine squamous syringometaplasia: Reappraisa of epidemiological, clinical, and pathological features

Antonio Martorell-Calatayud, MD,[a] Onofre Sanmartín, MD,[a] Rafael Botella-Estrada, MD,[a]
Nicole N. Balmer, MD,[b] Carlos Serra-Guillén, MD,[a] Elisabeth Gomez-Moyano, MD,[c] Victor Traves-Zapata, MD
Celia Requena, MD,[a] Eduardo Nagore, MD,[a] Beatriz Llombart-Cussac, MD,[a]
and Carlos Guillen-Barona, MD[a]
Valencia and Malaga, Spain; and Birmingham, Alabama

ORIGINAL ARTICLE

Chemotherapy-related bilateral dermatitis associated with eccrine squamous syringometaplasia: Reappraisal of epidemiological, clinical, and pathological features

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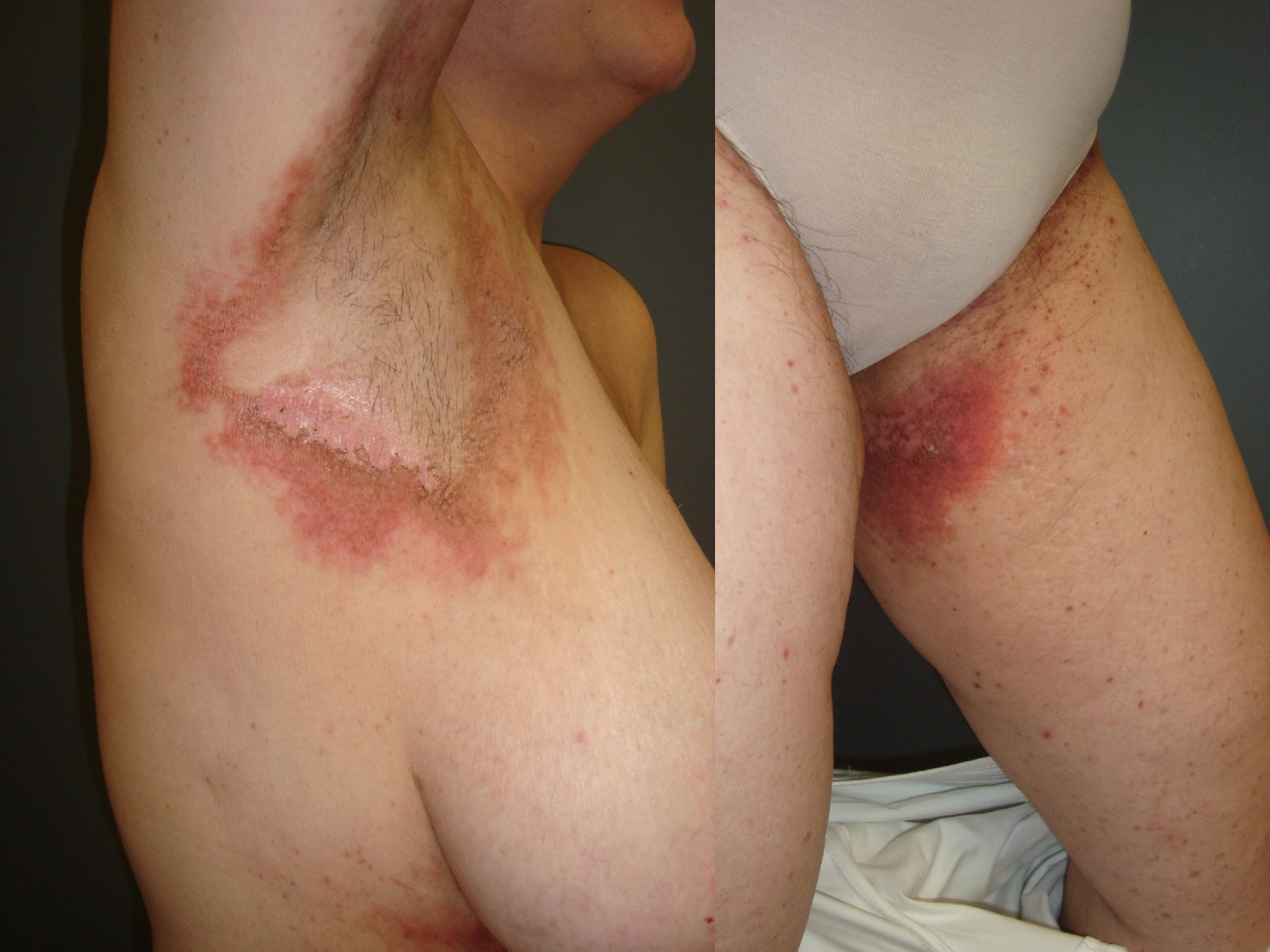
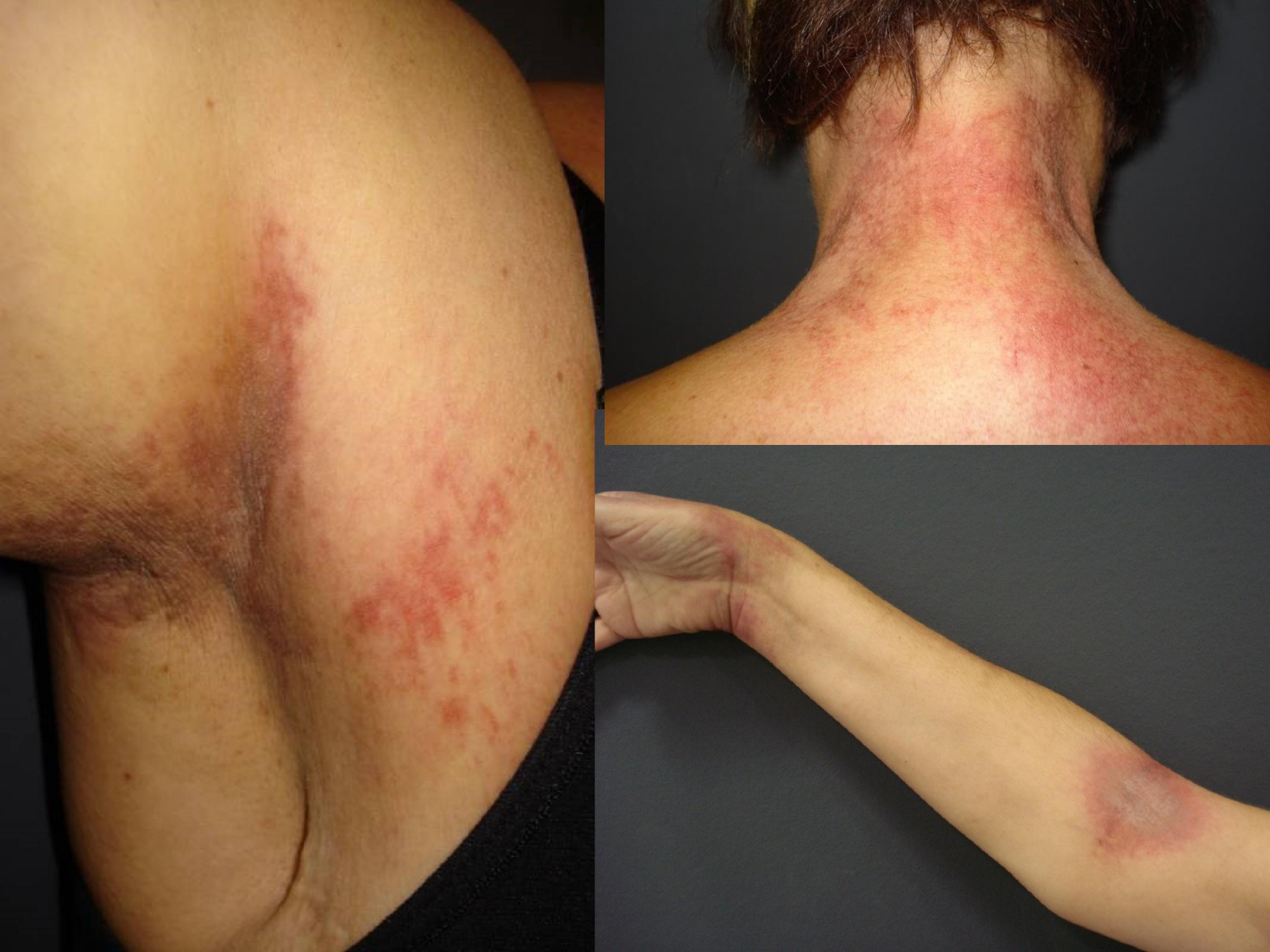
Valencia and Malaga, Spain; and Birmingham, Alabama

AGENTES CAUSANTES

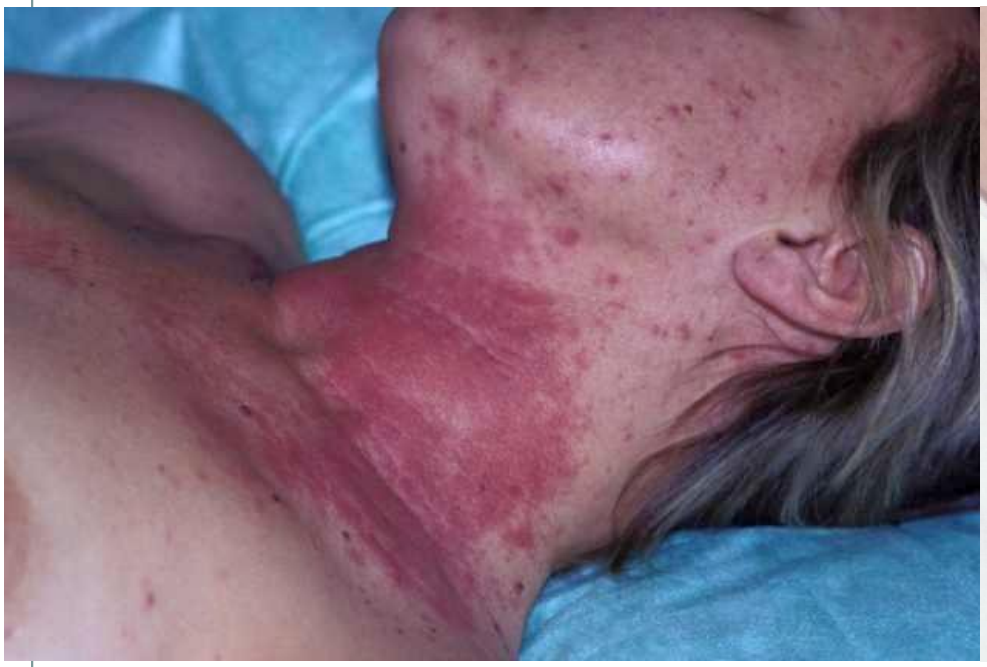
QT intensiva para TAMO
Liposomal doxorubicina
Docetaxel
Temsirolimus, deferolimus
Vemurafenib

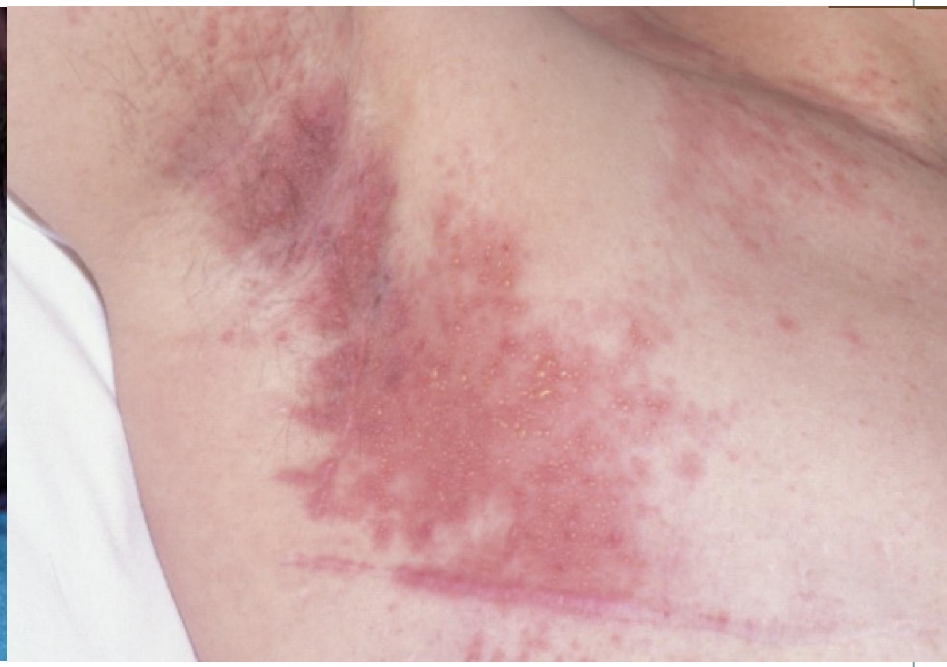
J Am Acad Dermatol. 2011 Jun;64(6):1092-103





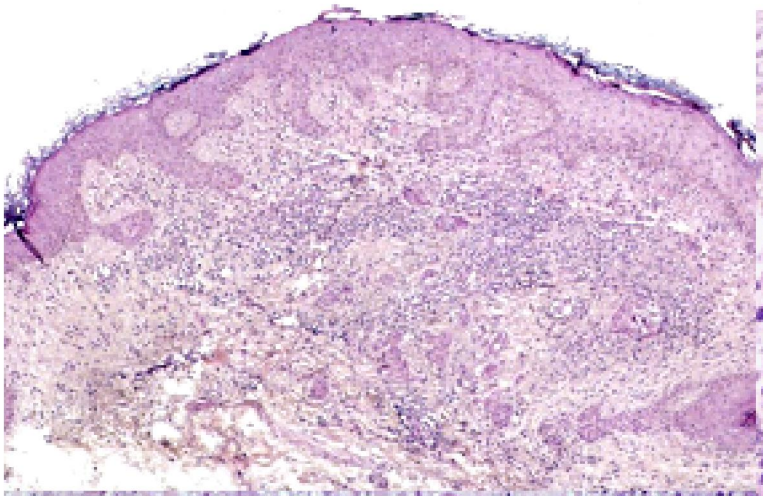
Siringometaplasia escamosa ecrina

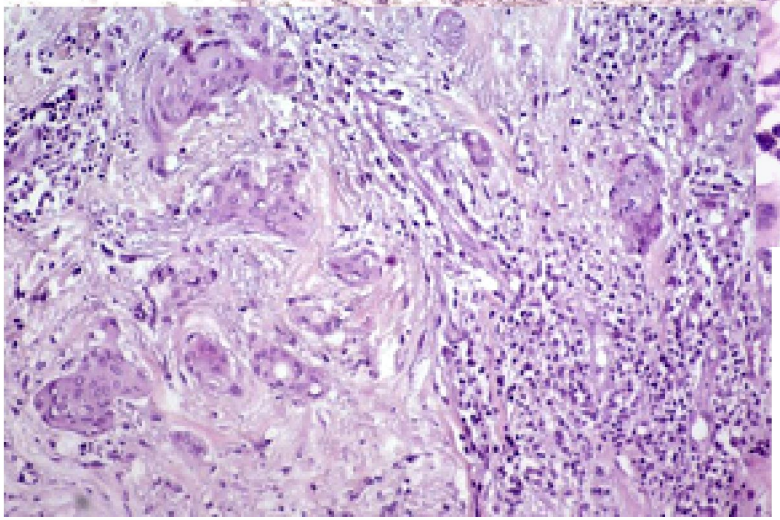


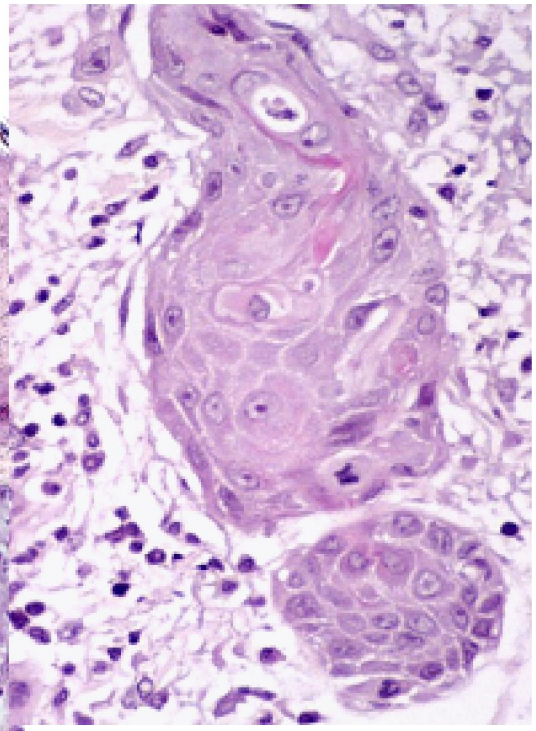


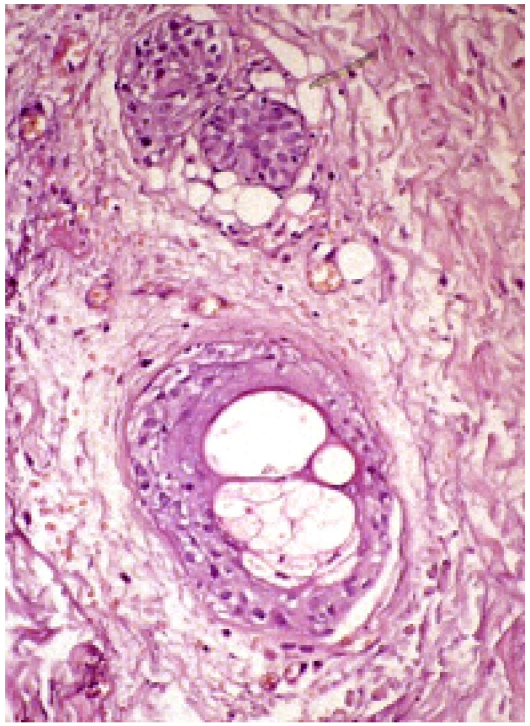
- Eritema, edema y vesiculación en cuello, axilas, ingles y región lumbosacra

Siringometaplasia escamosa ecrina



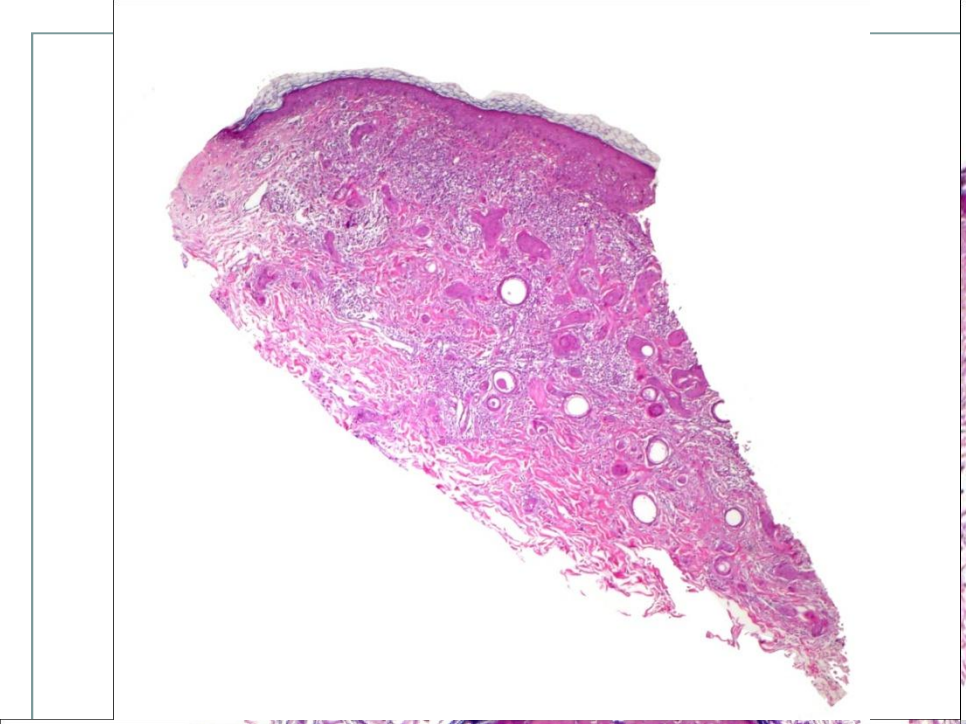
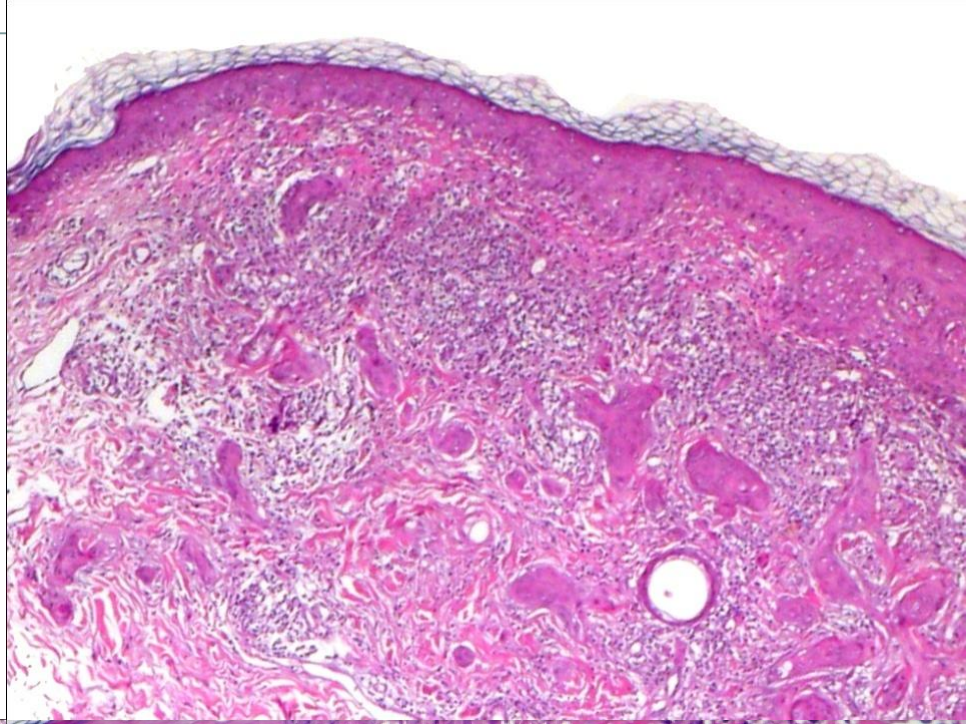
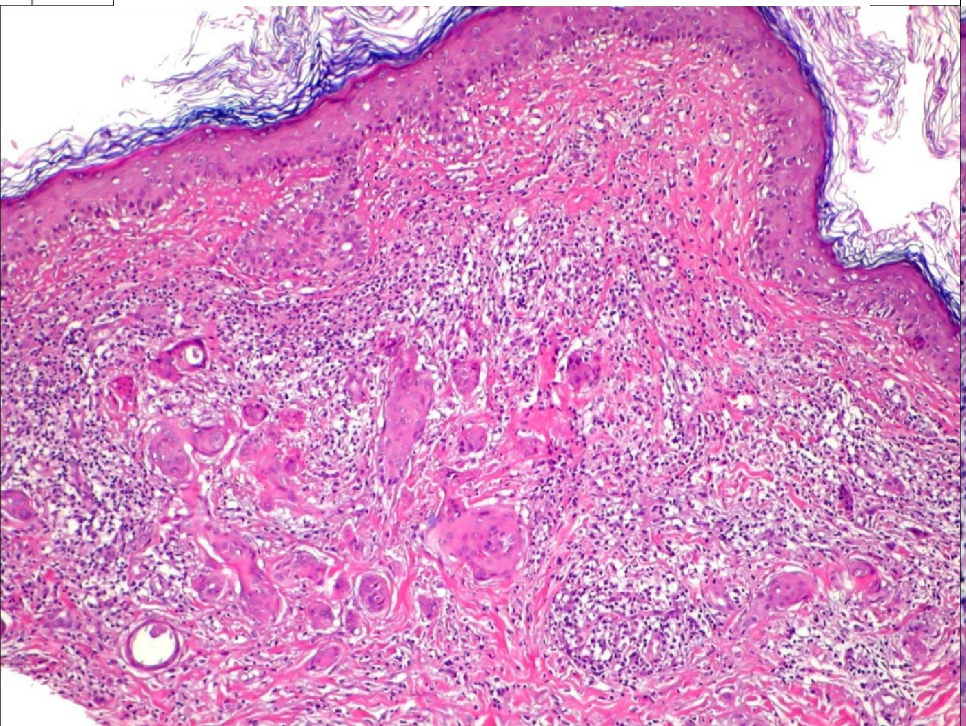
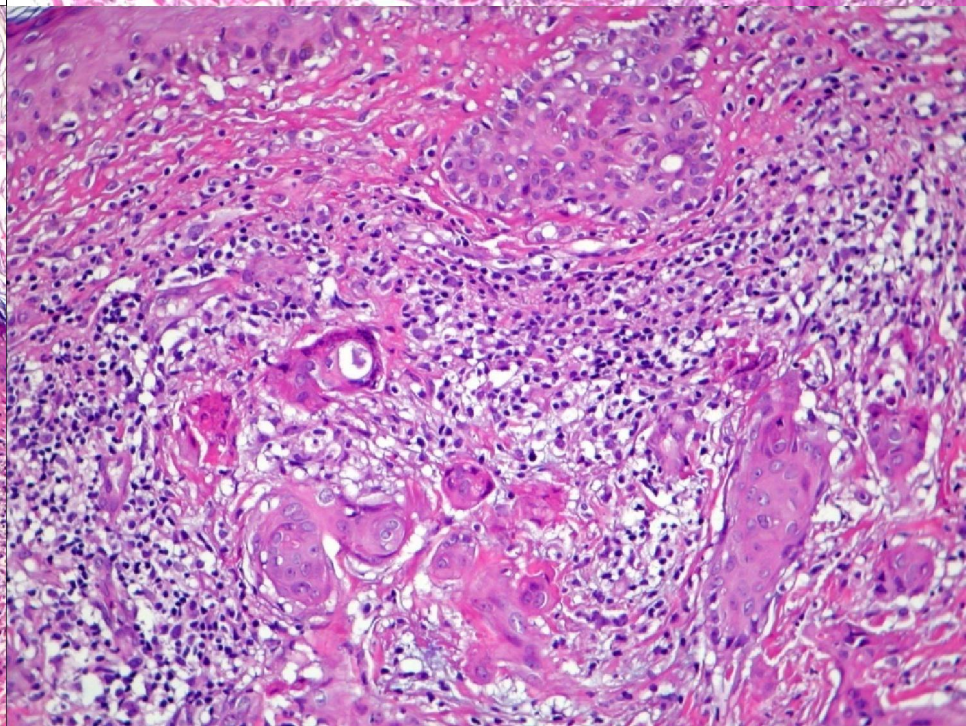






SMEE madura.

Ectasia ductal, proliferación ductal, Figuras mitóticas, queratinización, pseudomalignidad

¿Producen los agentes antidiana afectación epidérmica?

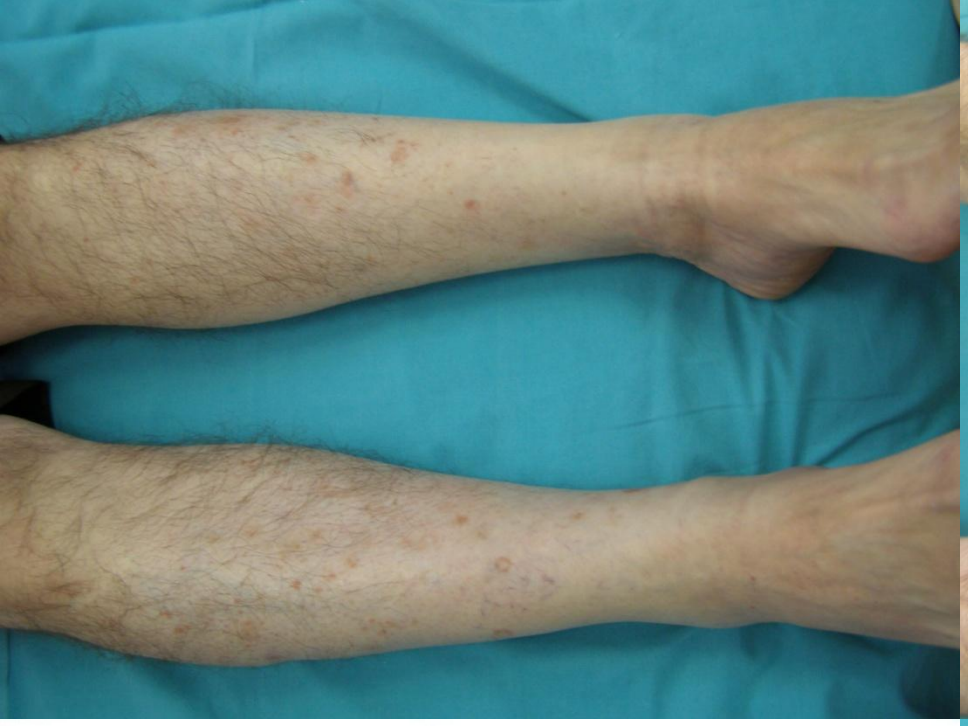
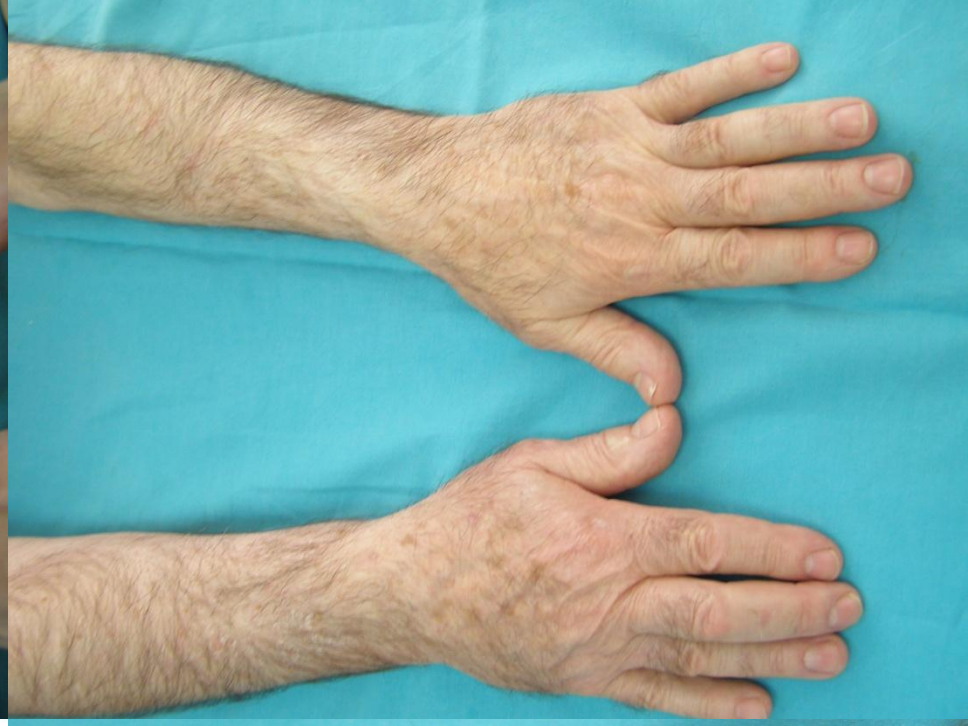
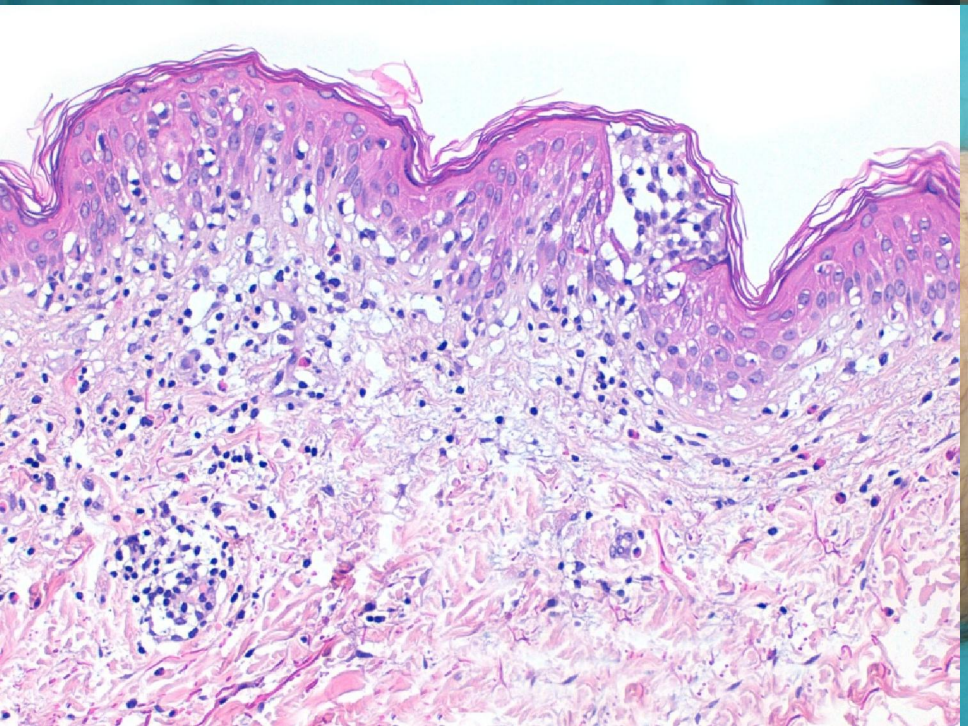
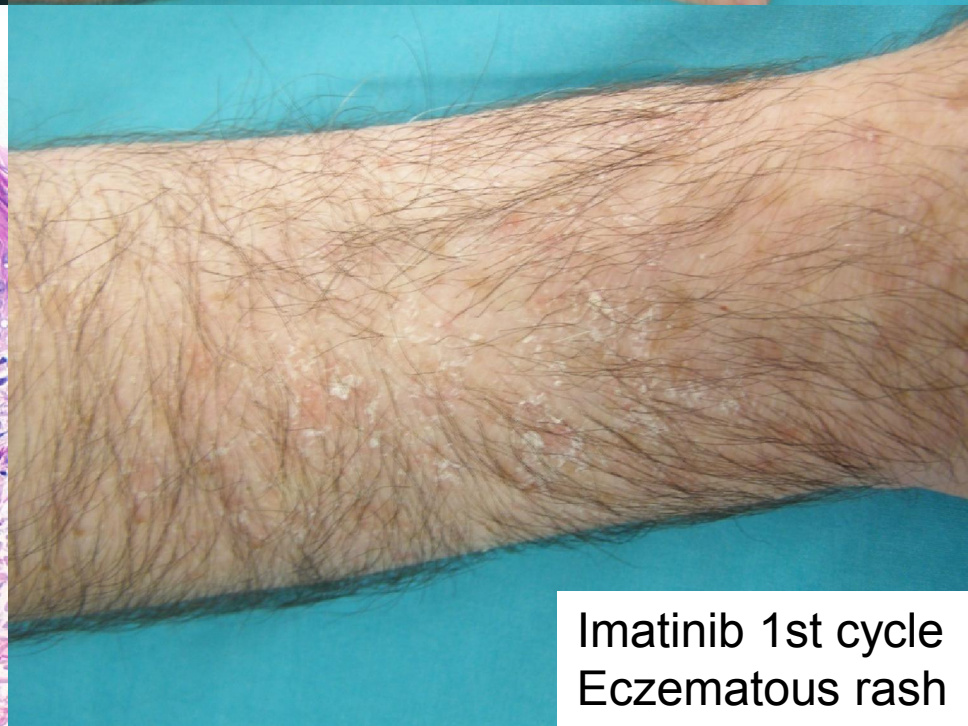
- La respuesta es SI
- Pero hay claras diferencias con el patrón de citotoxicidad epidérmica inducida por la quimioterapia
- La patogénesis está relacionada con la inhibición de vías de señalización celular en la epidermis, cuya función fisiológica es desconocida actualmente
- La histopatología es diferente

RASH POR INHIBIDORES MULTIKINASA

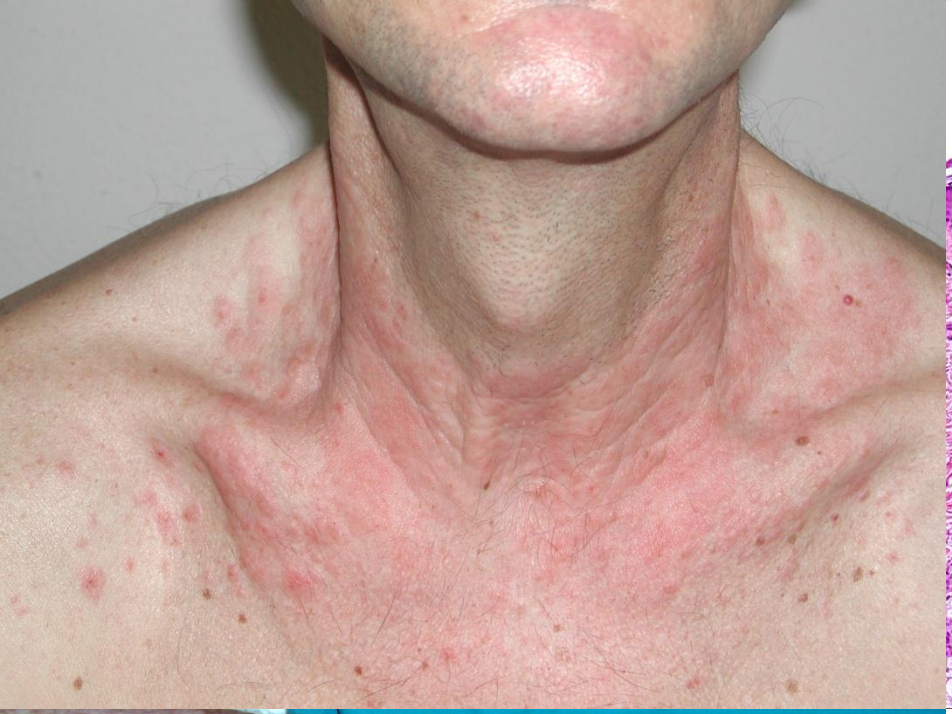
- Exantemas dosis dependiente
- No correlación con la eficacia (a diferencia de la erupción acneiforme de los inhibidores del EGFR)
- Más frecuente con imatinib (30% of pts), sunitinib (15% of pts), sorafenib (27%), vemurafenib (15%)
- Posiblemente se deba a la inhibición de c-kit o componentes distales de la via MAPK

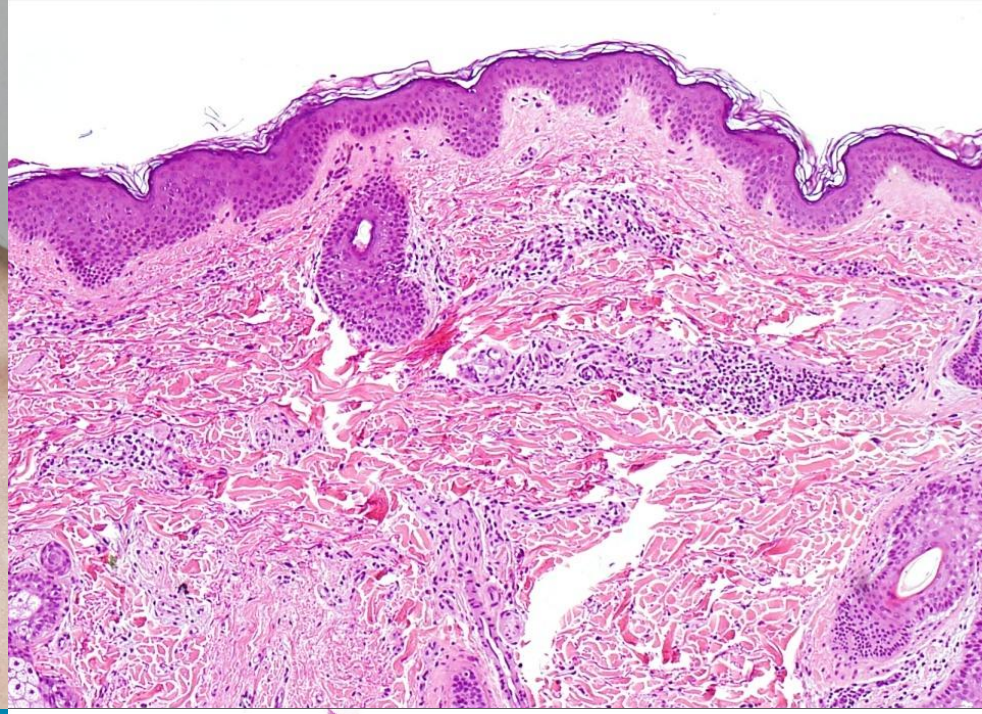
RASH POR INHIBIDORES MULTIKINASA

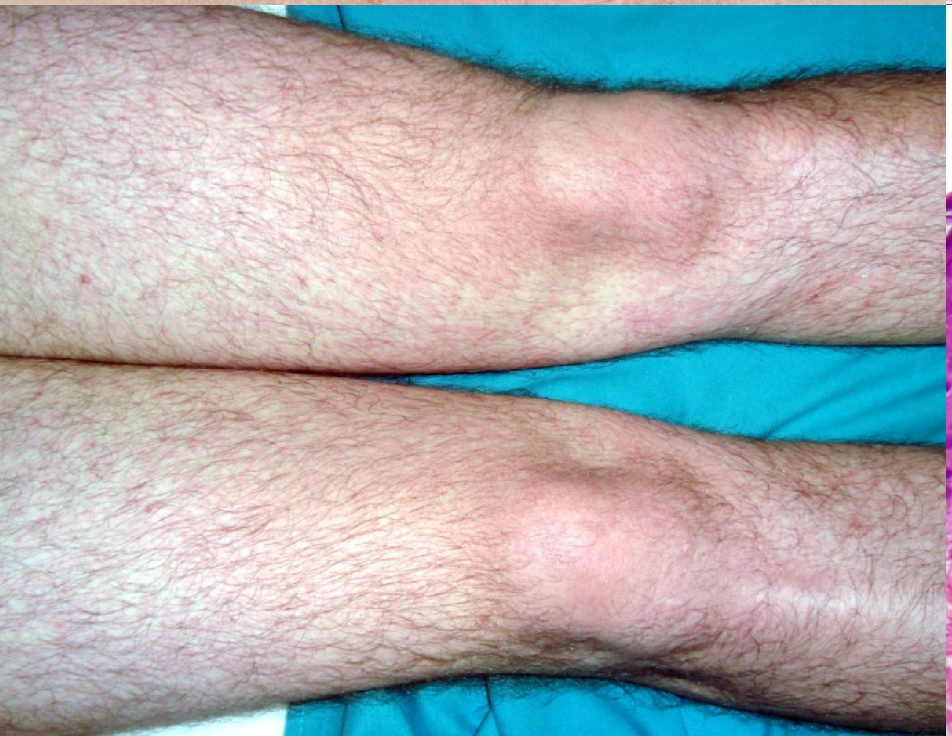
- Primeras semanas de tratamiento
- Exantema.
  - Máculo-papular generalmente
  - Ocasionalmente erupción pustular
- Tronco y extremidades, menor frecuencia por afectación de pliegues
- Intensamente pruriginoso, ocasionalmente doloroso

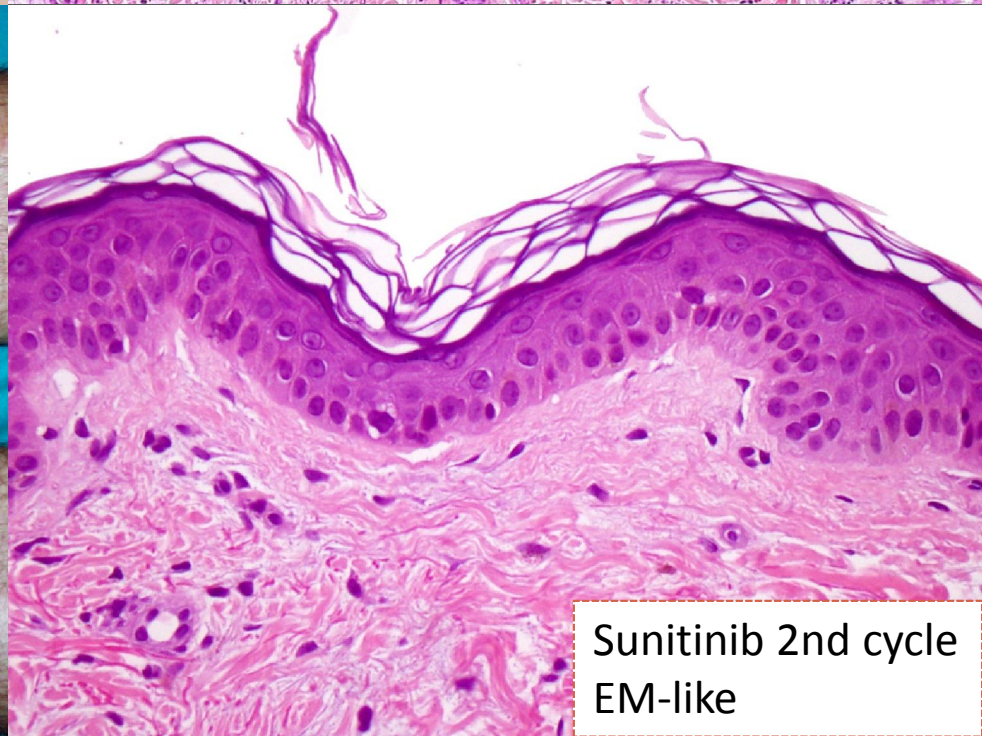





Imatinib 1st cycle
Eczematous rash

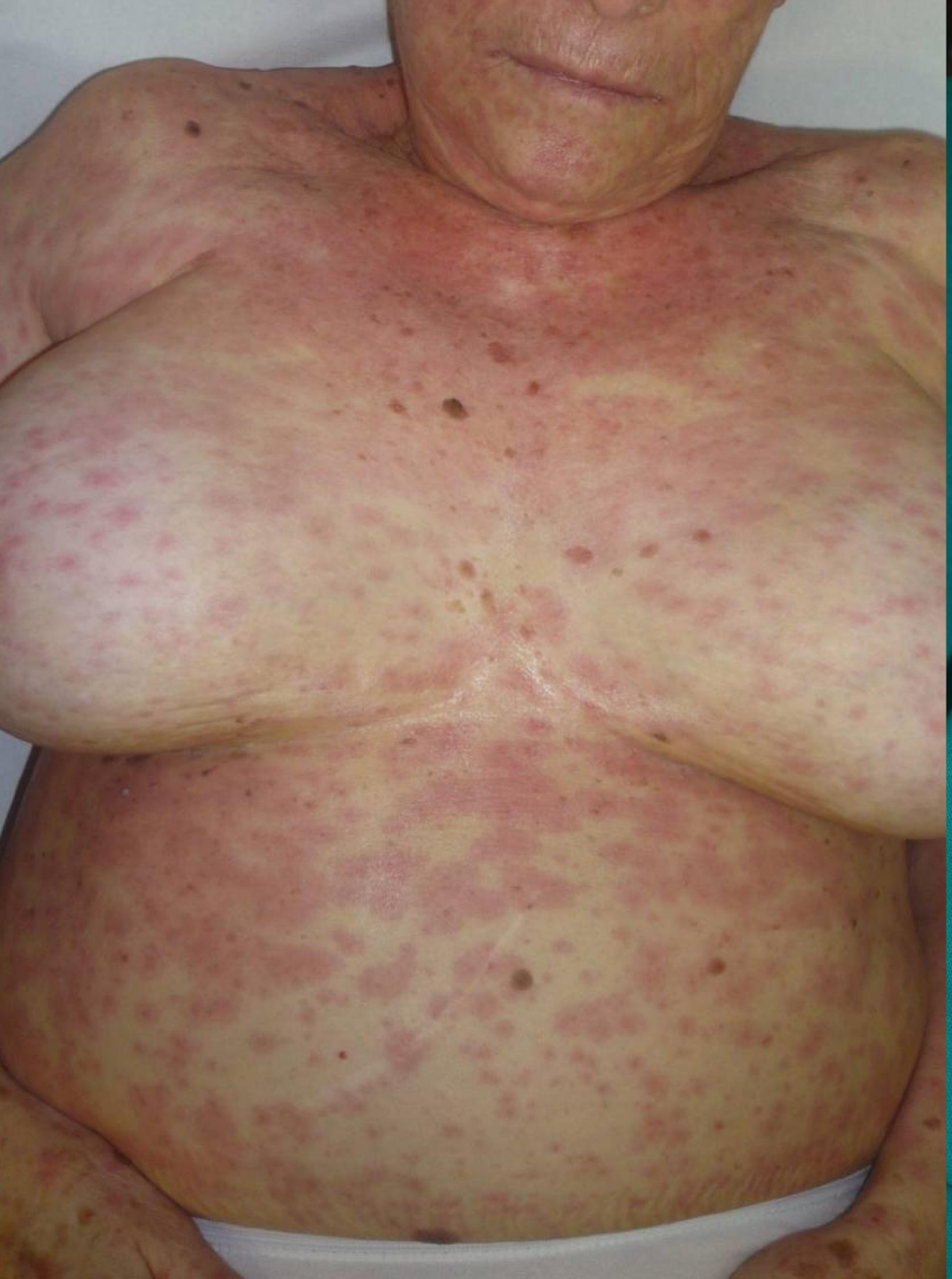


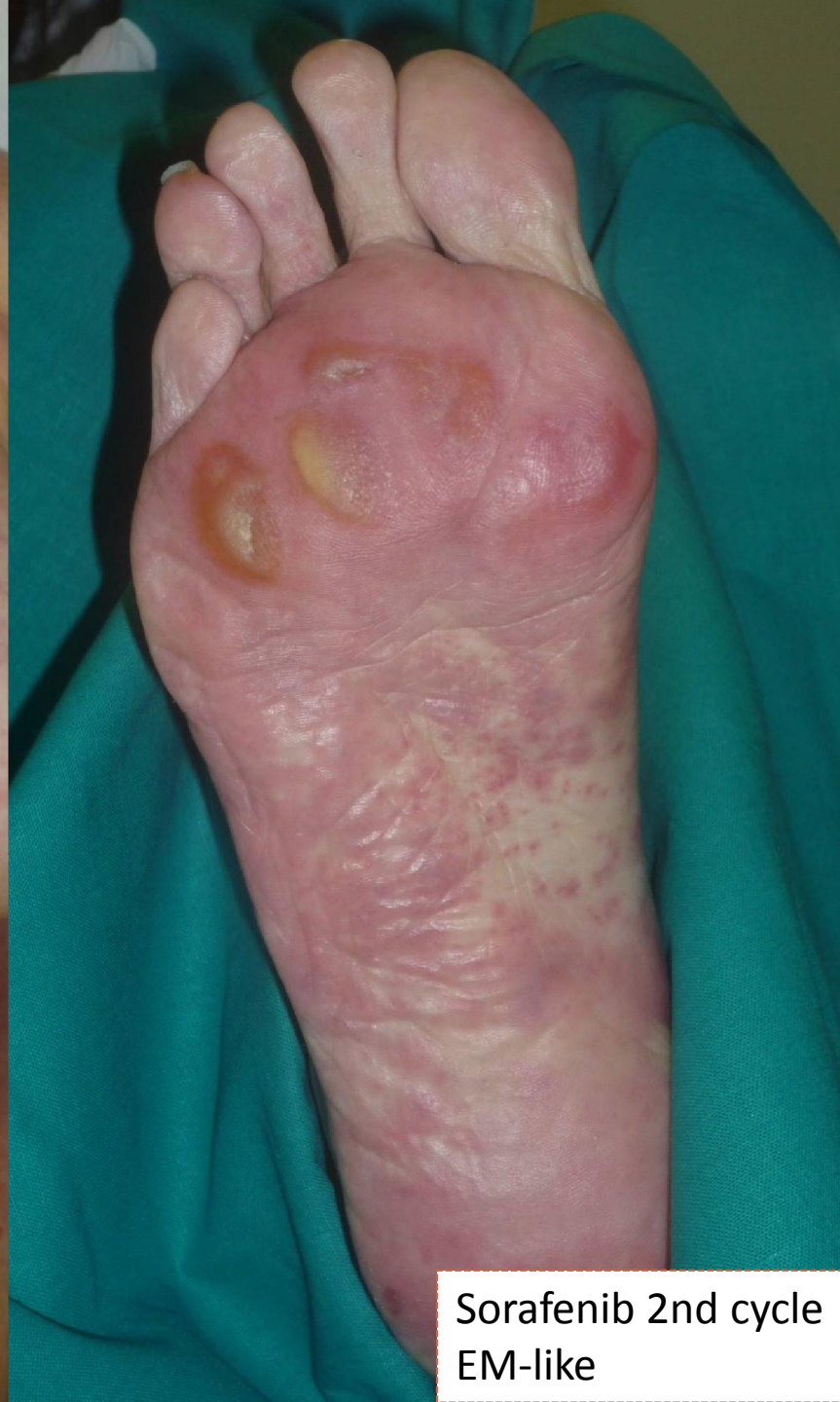




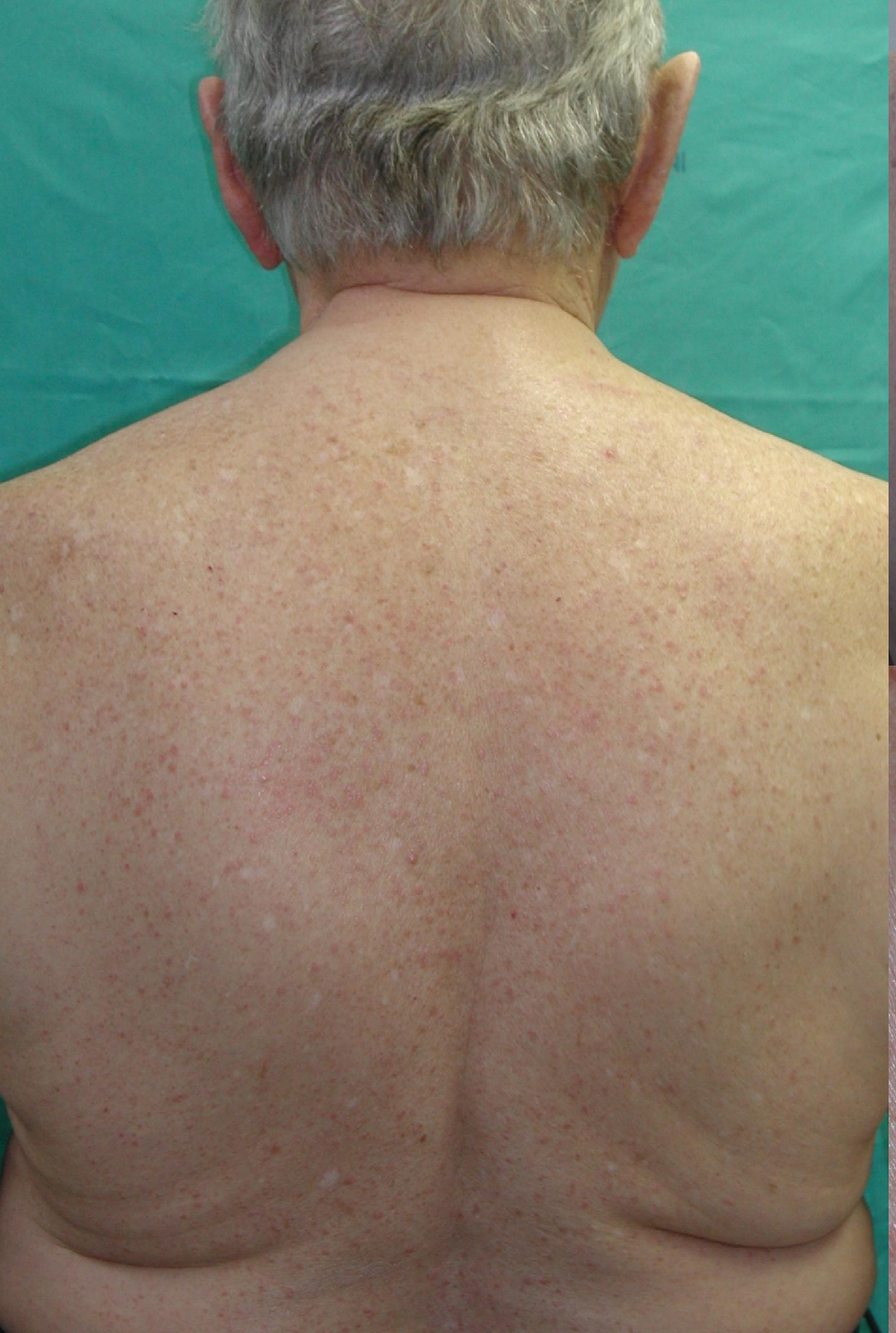


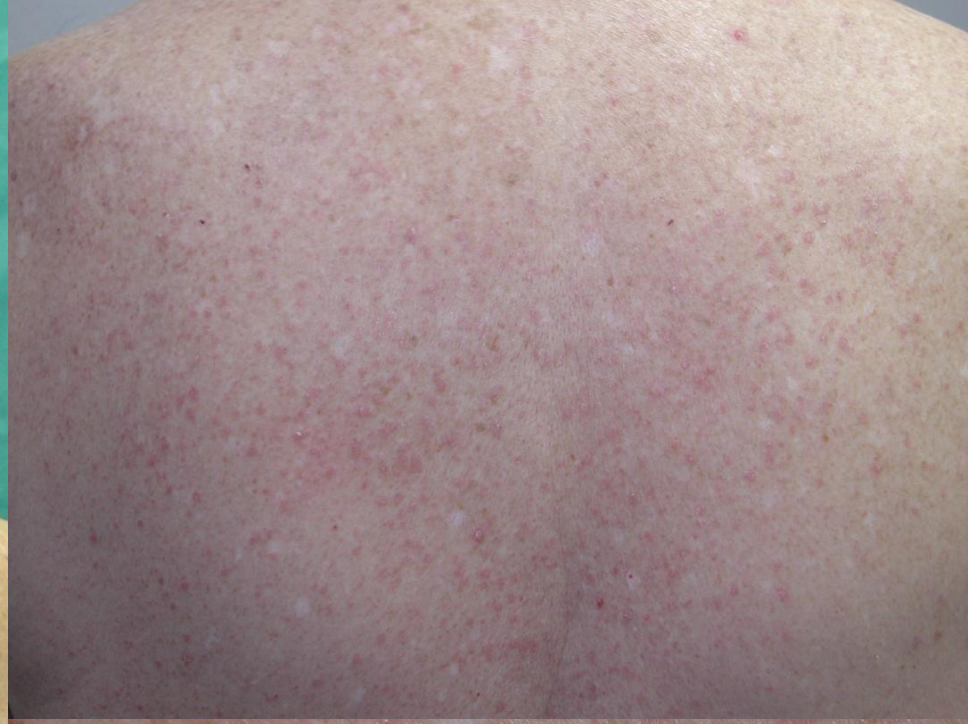
Sunitinib 2nd cycle
EM-like

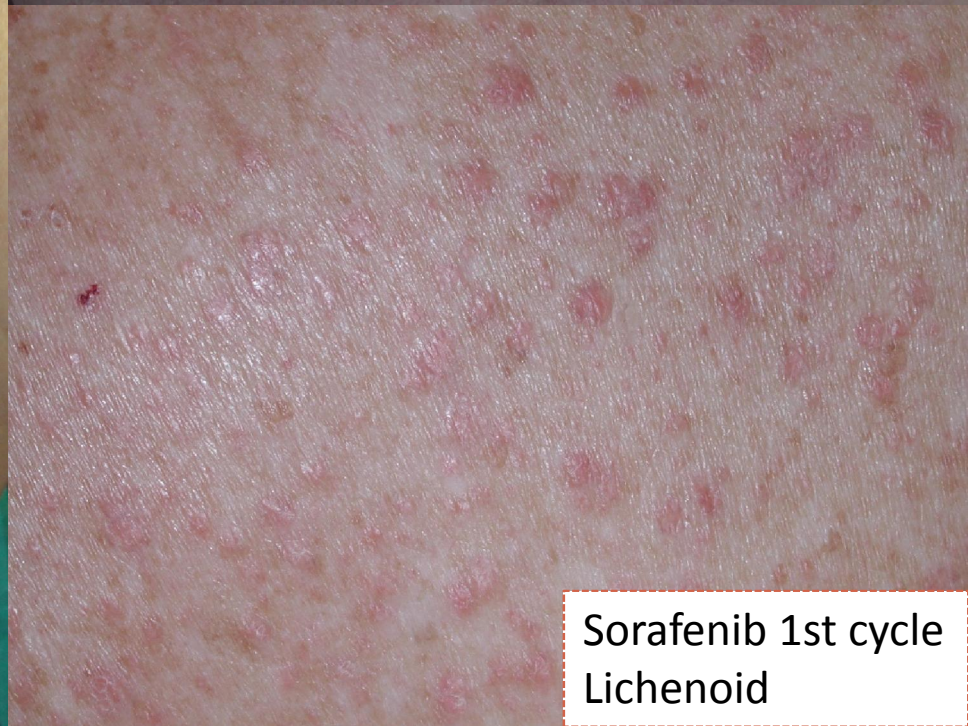




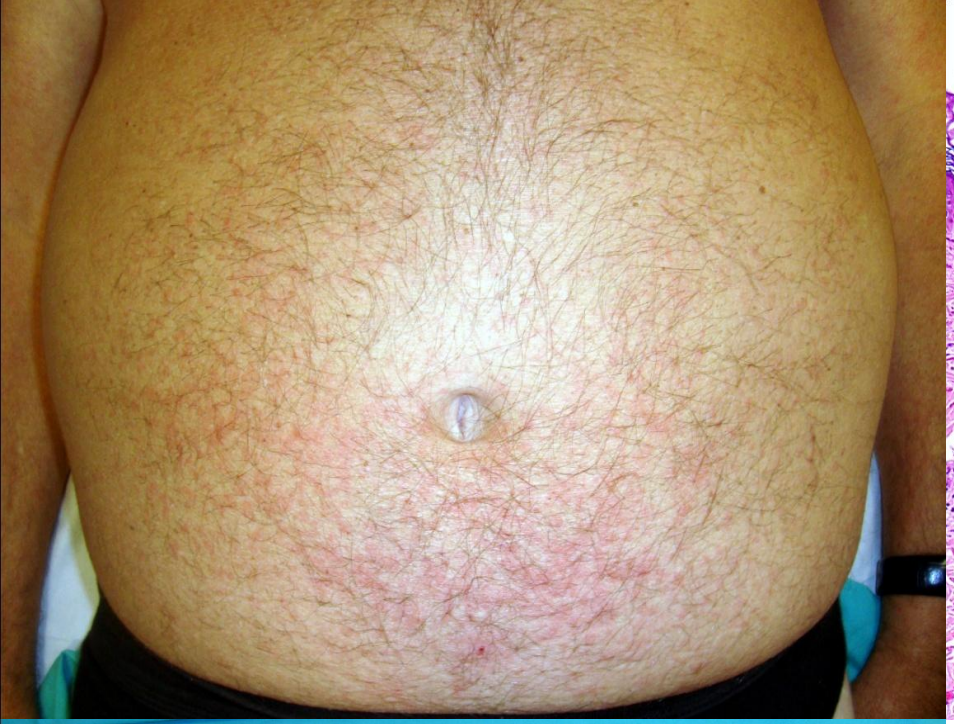
Sorafenib 2nd cycle
EM-like

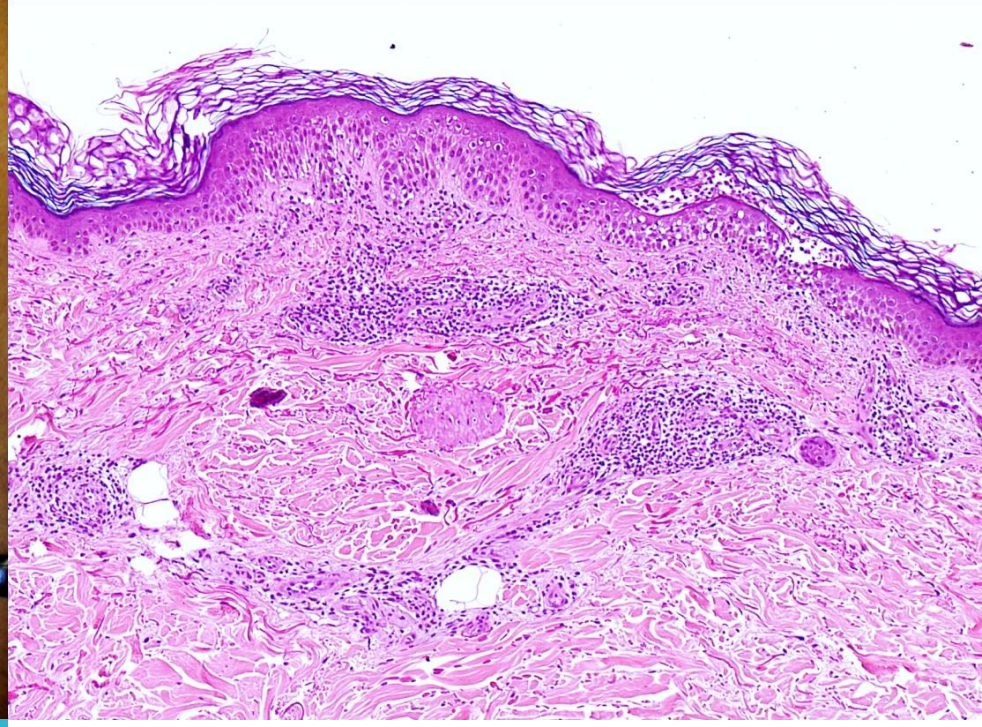


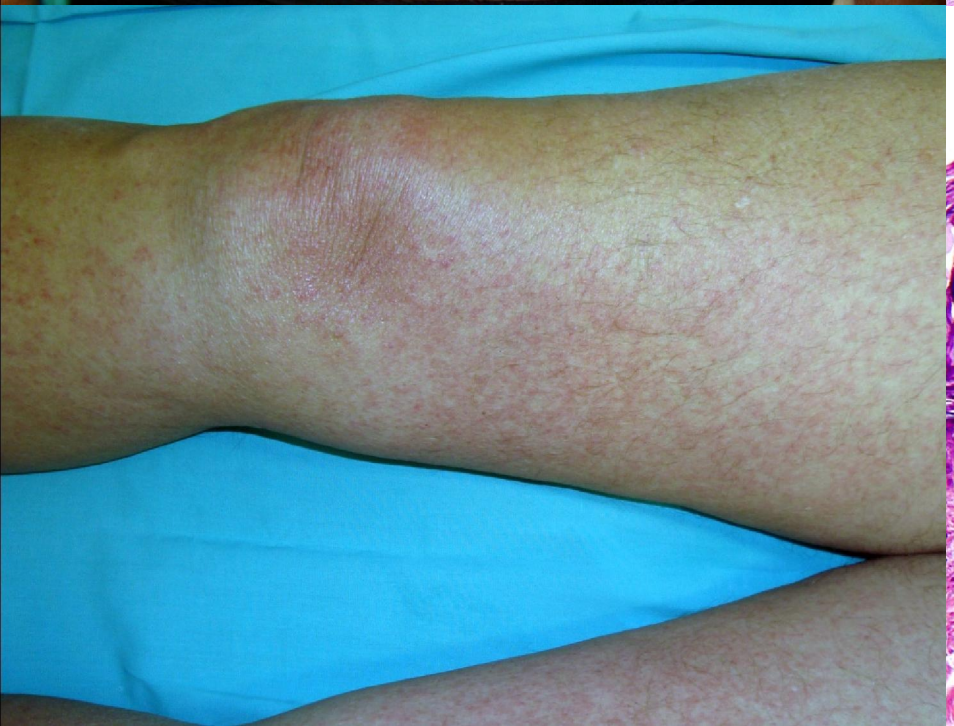


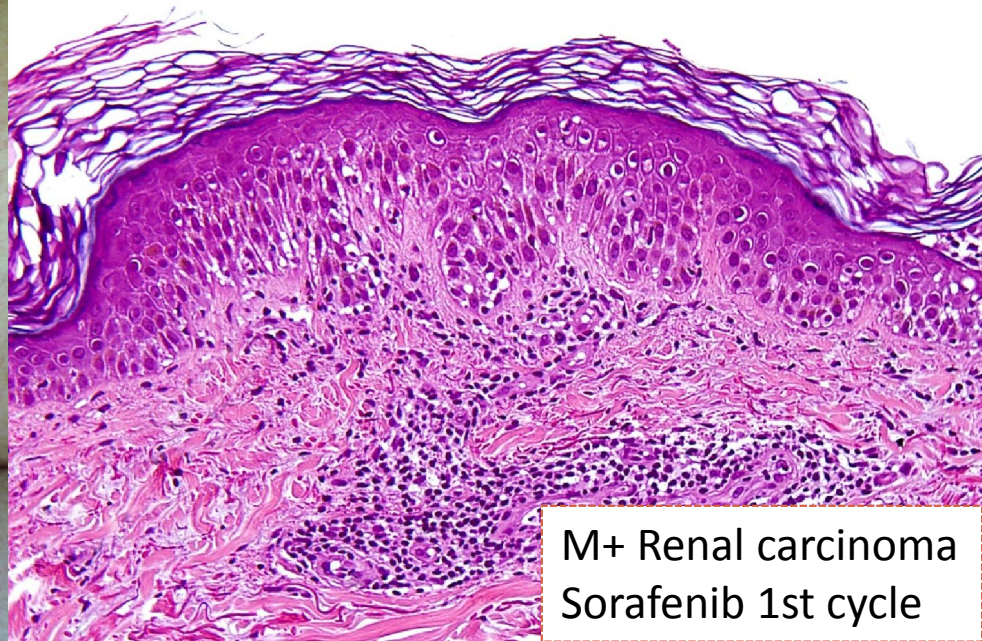


Sorafenib 1st cycle
Lichenoid

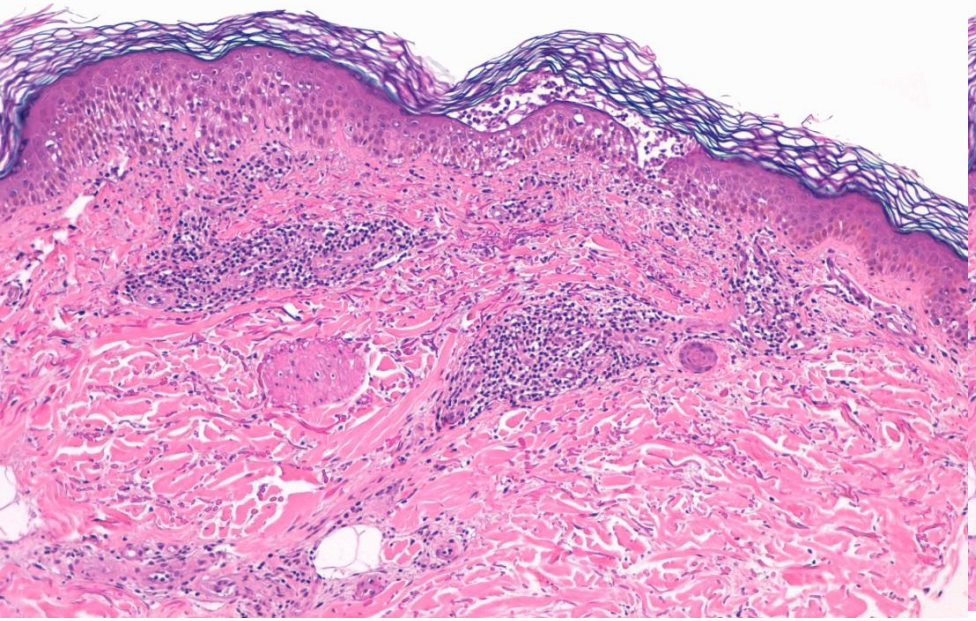
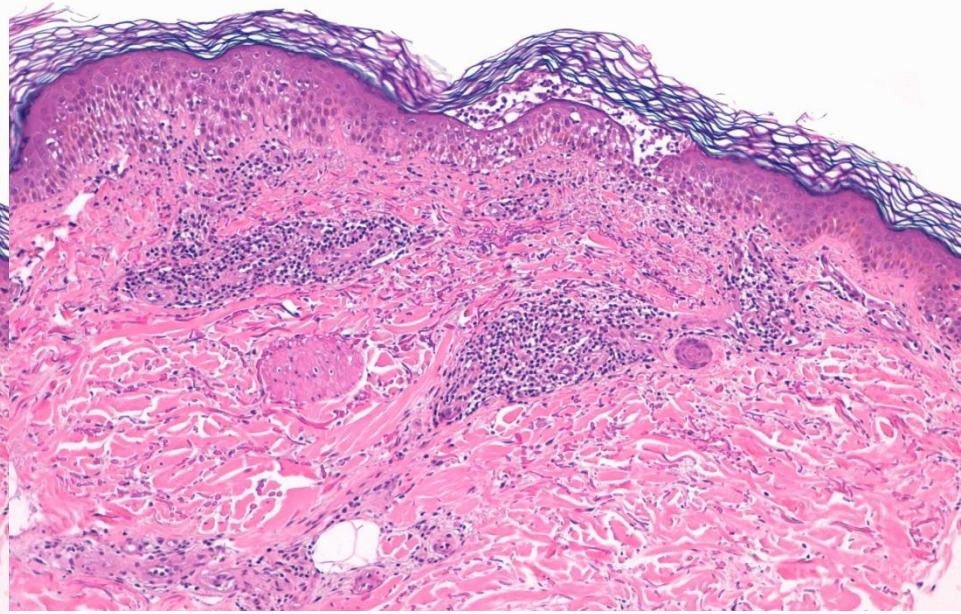
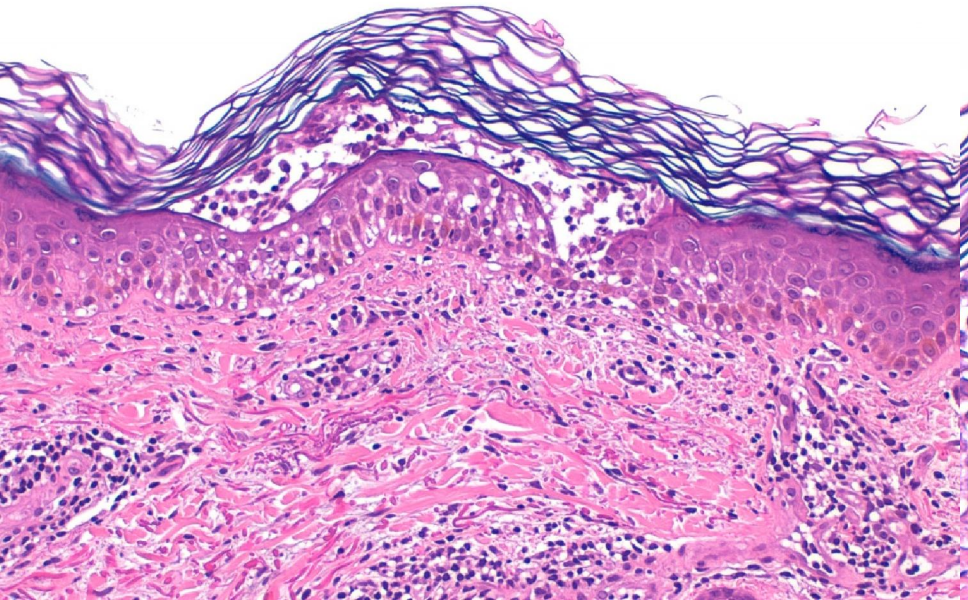
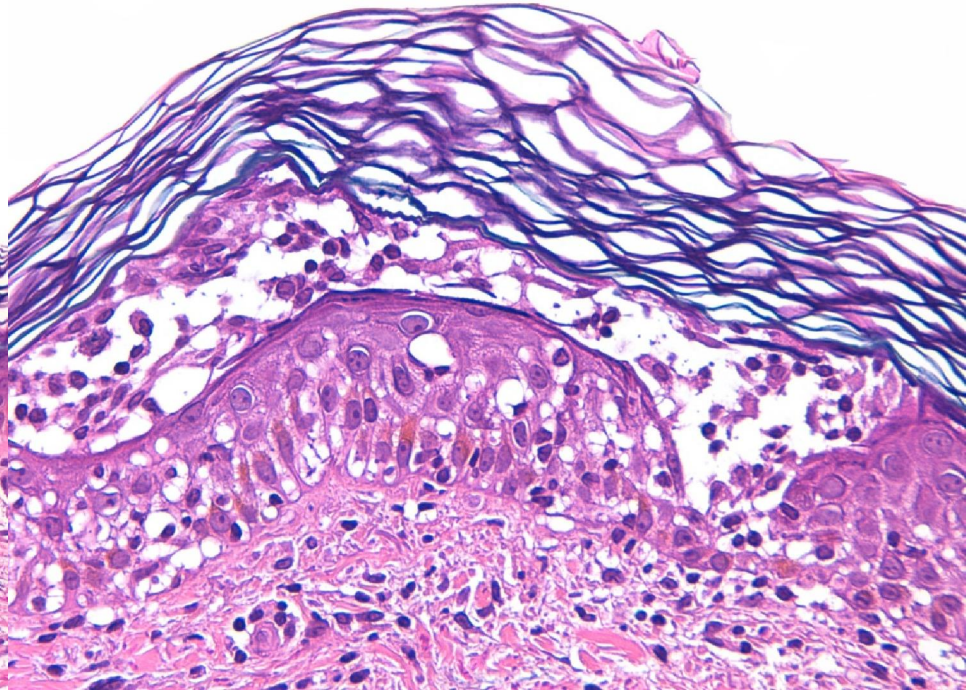


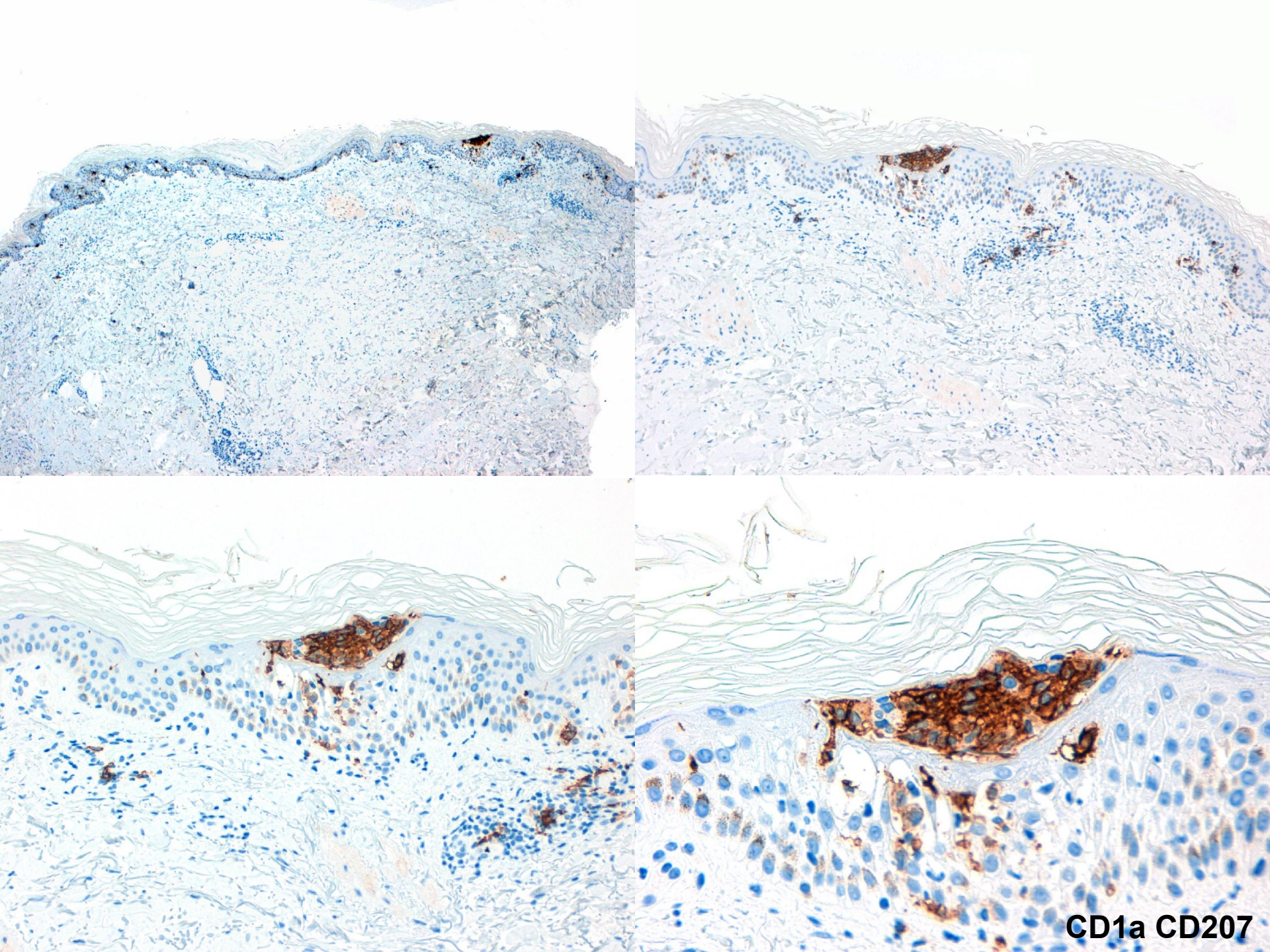






M+ Renal carcinoma
Sorafenib 1st cycle


CD1a CD207

RASH POR INHIBIDORES MULTIKINASA

- Tendencia a la resolución con la progresión del tratamiento
- NO requiere suspender el mismo, quizás ajuste de la dosis temporalmente
- Antihistaminicos y corticoides tópicos
- Ninguna correlación con la respuesta al tratamiento

REACCIONES ACNEIFORMES

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

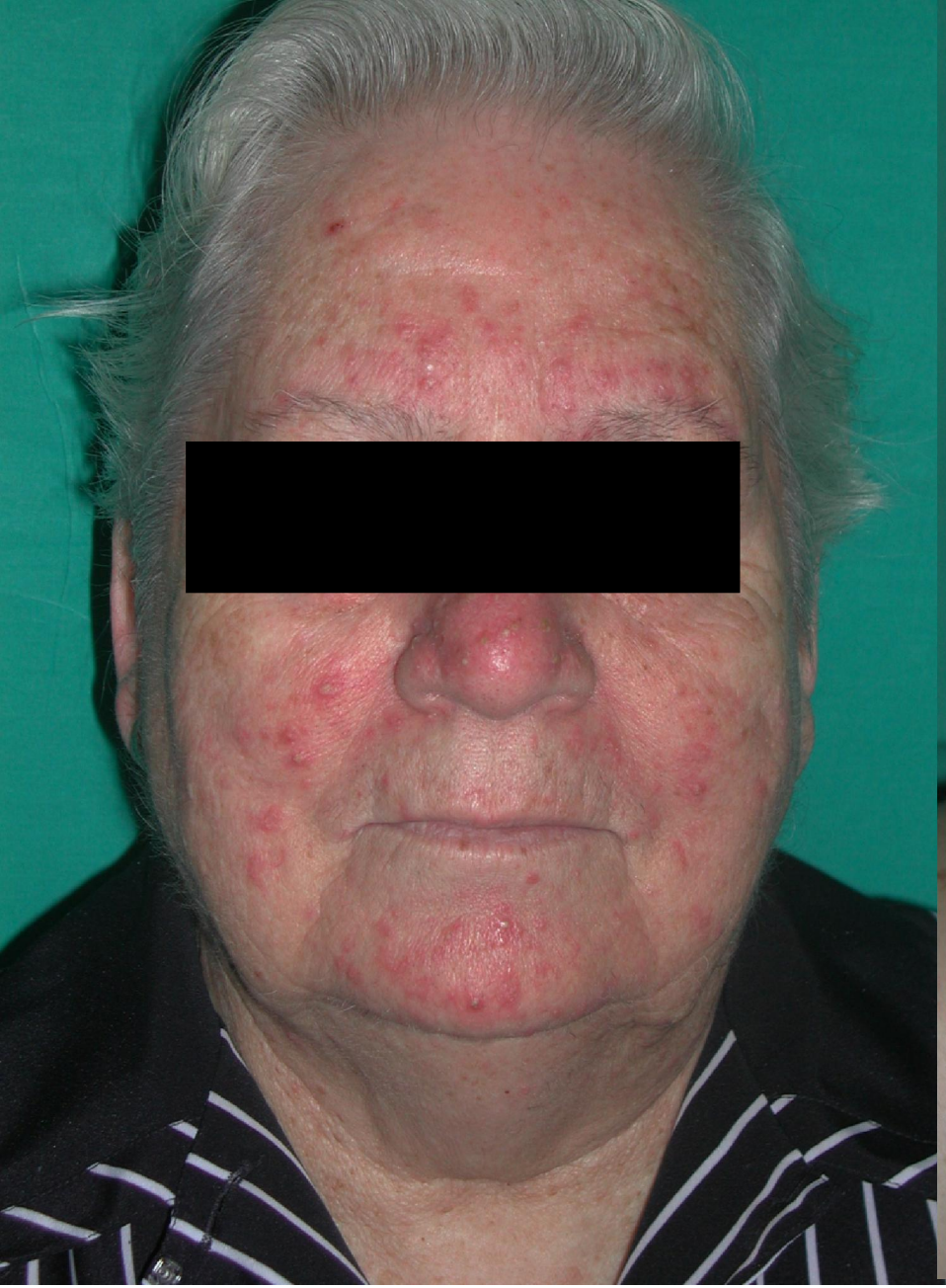
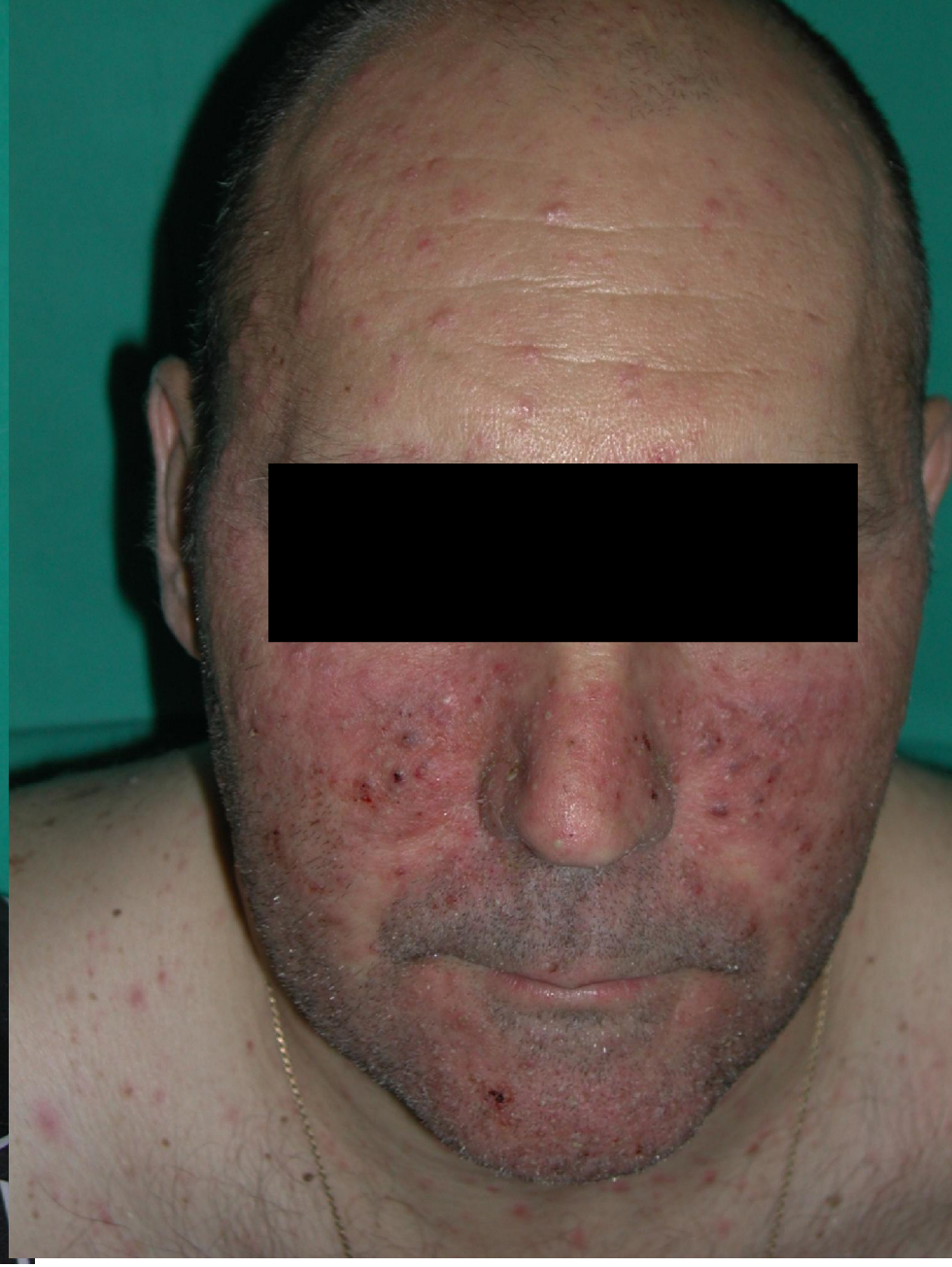
Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	1	2	3	4	
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	
Definition: A disorder characterized by an intense itching sensation.					
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker pu and eventually become a brownish-yellow color.					
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.					

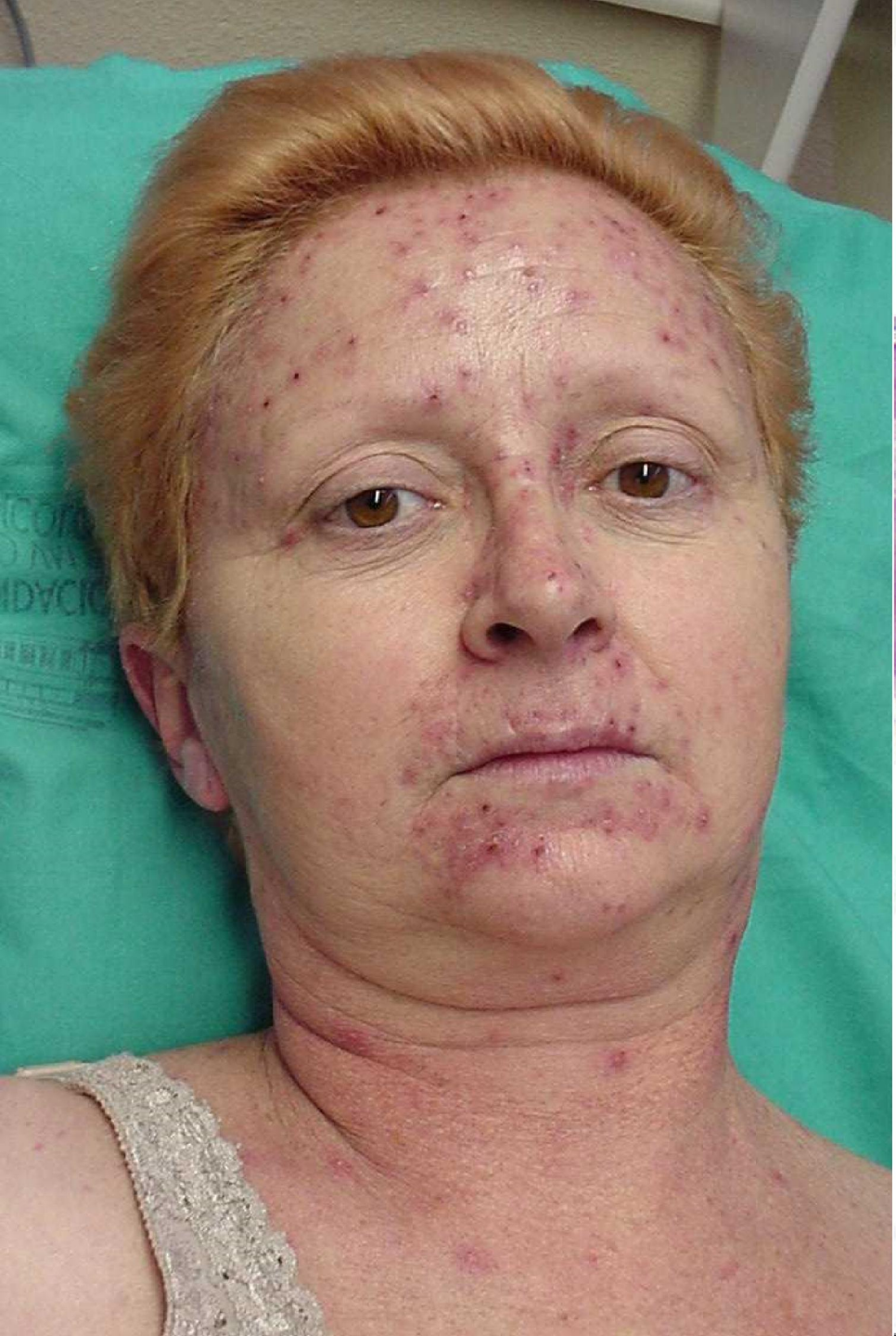



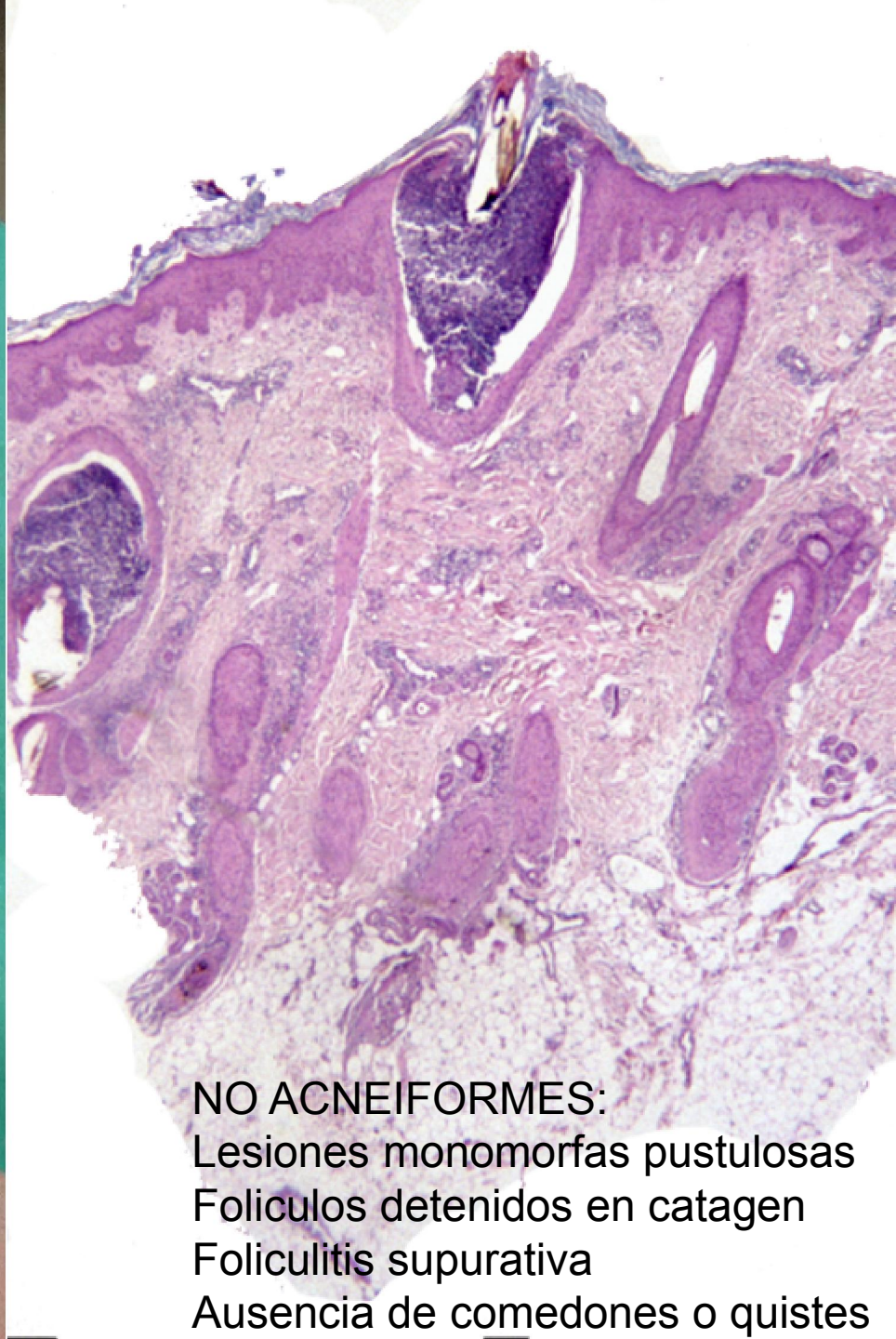
Reacciones acneiformes

- Efecto secundario mejor conocido de los ttos antidiana
- INHIBIDORES DEL EGFR:
  - Anticuerpos monoclonales: Cetuximab, Panitumumab
  - Inhibidores Tirosin-Kinasa:
    - HER1: erlotinib, gefitinib, vandetanib
    - HER1/HER2 afatinib, lapatinib, neratinib
- INHIBIDORES mTOR
  - Everolimus, Temsirolimus

Reacciones acneiformes

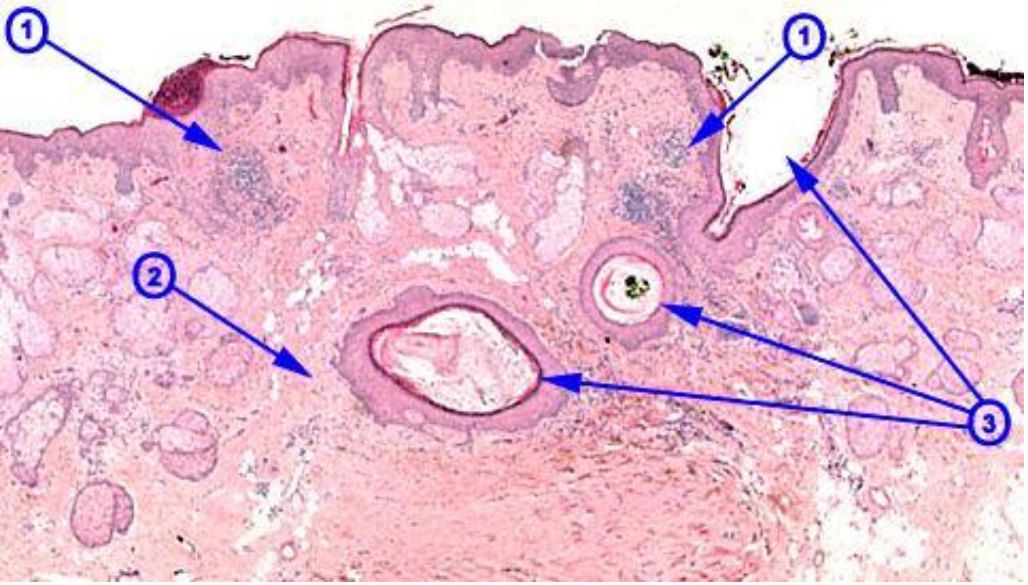
- Lesiones pustulosas monomorfas que con el tiempo evolucionan a lesiones eccematosas
- Cara >> tronco
- Dosis dependiente, intensidad relacionada con la respuesta
- EL RASH ACNEIFORME NO ES ACNE
- REALMENTE ES UNA FOLICULITIS

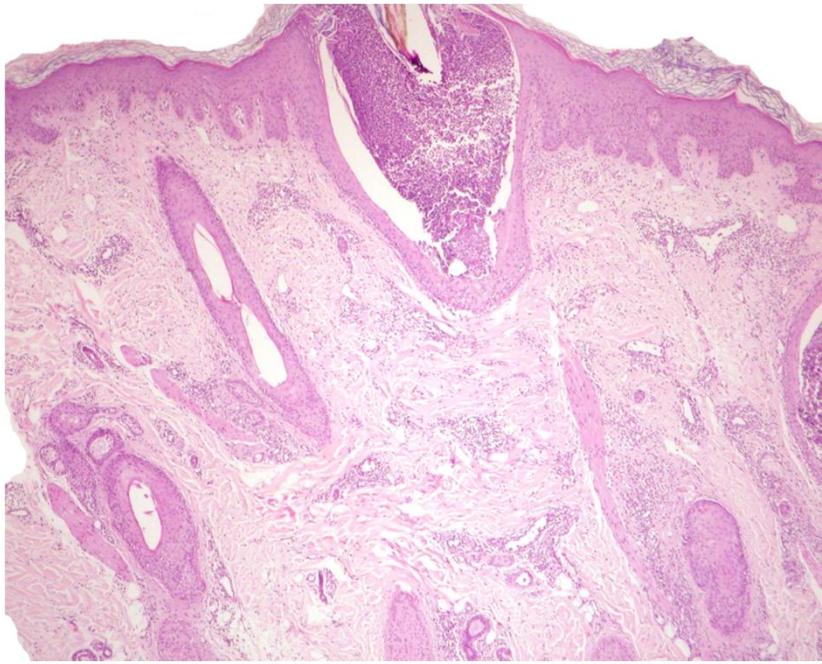




NO ACNEIFORMES:
Lesiones monomorfas pustulosas
Foliculos detenidos en catagen
Foliculitis supurativa
Ausencia de comedones o quistes

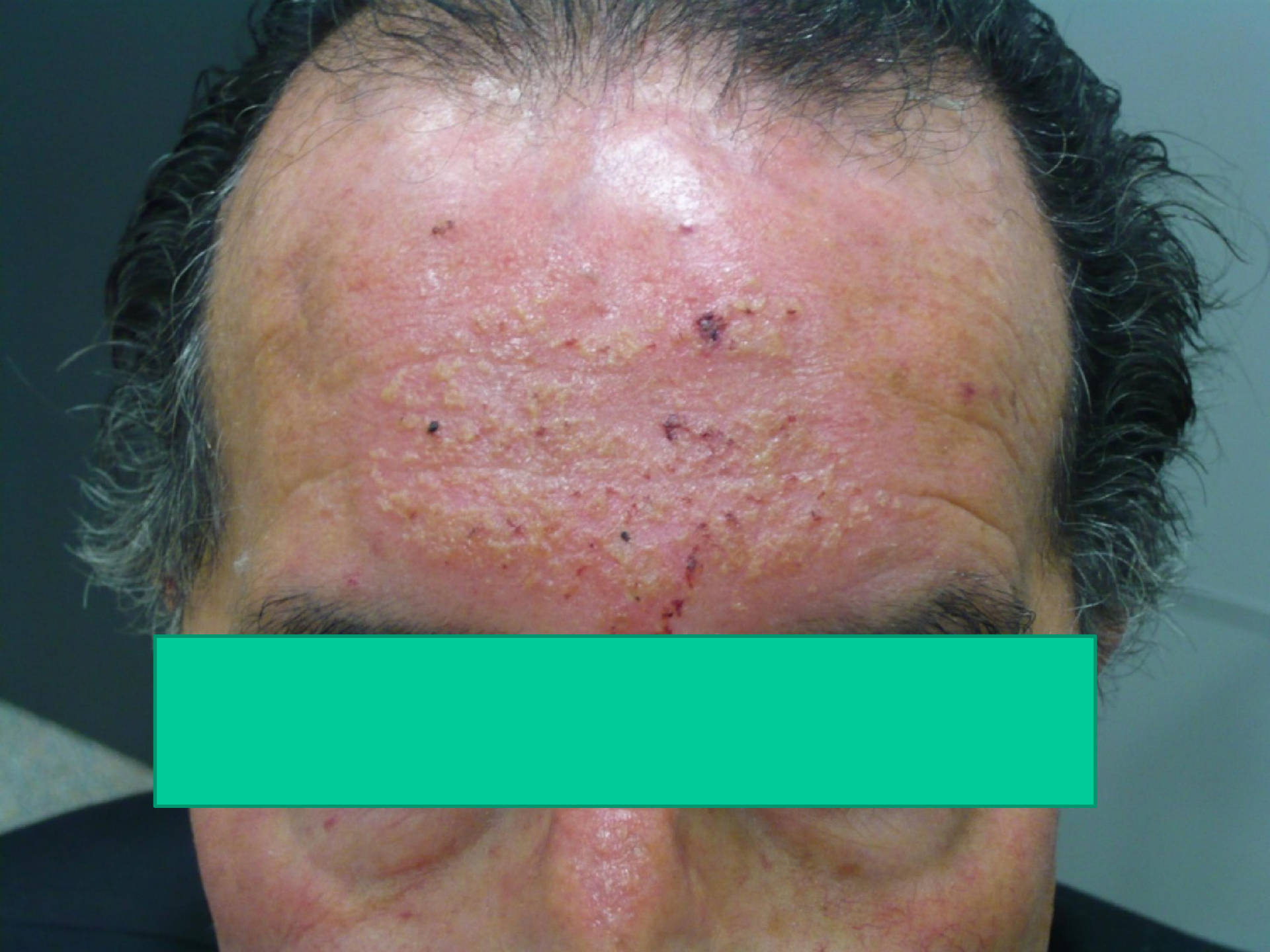
NO ES ACNE





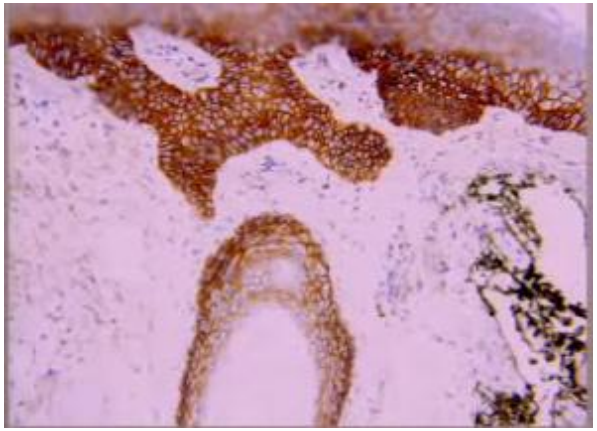
NO ES INFECCION

- Pústulas estériles o con flora saprofita
- NO obstante la sobreinfección es posible
- Cultivar todas aquellas lesiones sospechosas
- J Nat Cancer Inst 2010; 102: 47-53
  - Análisis retrospectivo de 221 pacientes
  - 84 (38%) con evidencia de sobreinfeccion
  - Generalmente S aureus



Foliculitis por inhibidores de EGFR

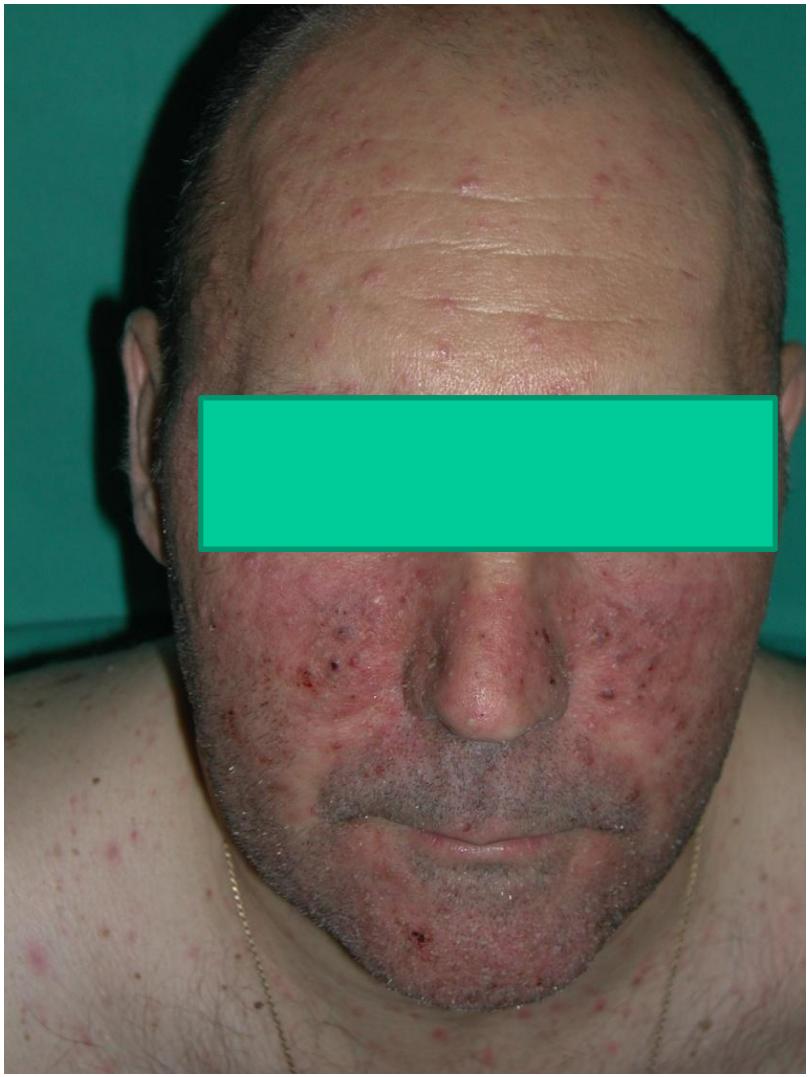
- Se expresa en epidermis, glándulas sebáceas, tejido periungueal y epitelio del folículo piloso
- Estimula el crecimiento epidérmico
- Inhibe diferenciacion

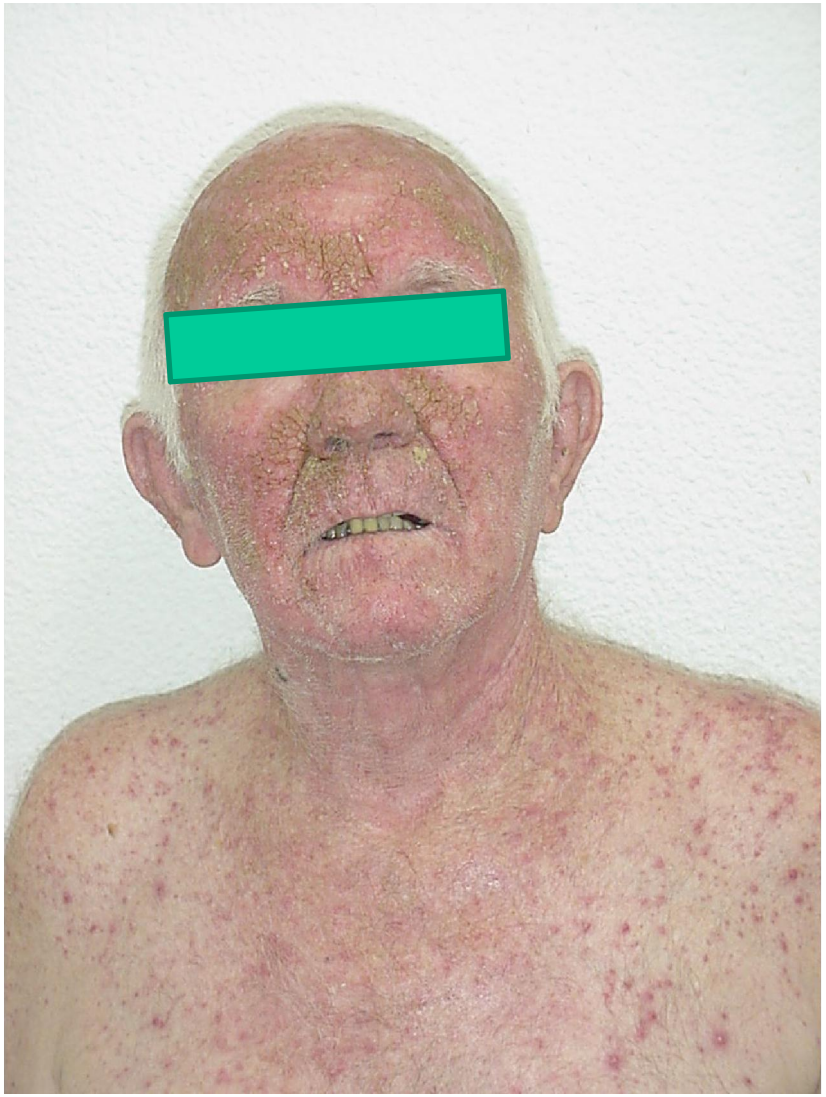


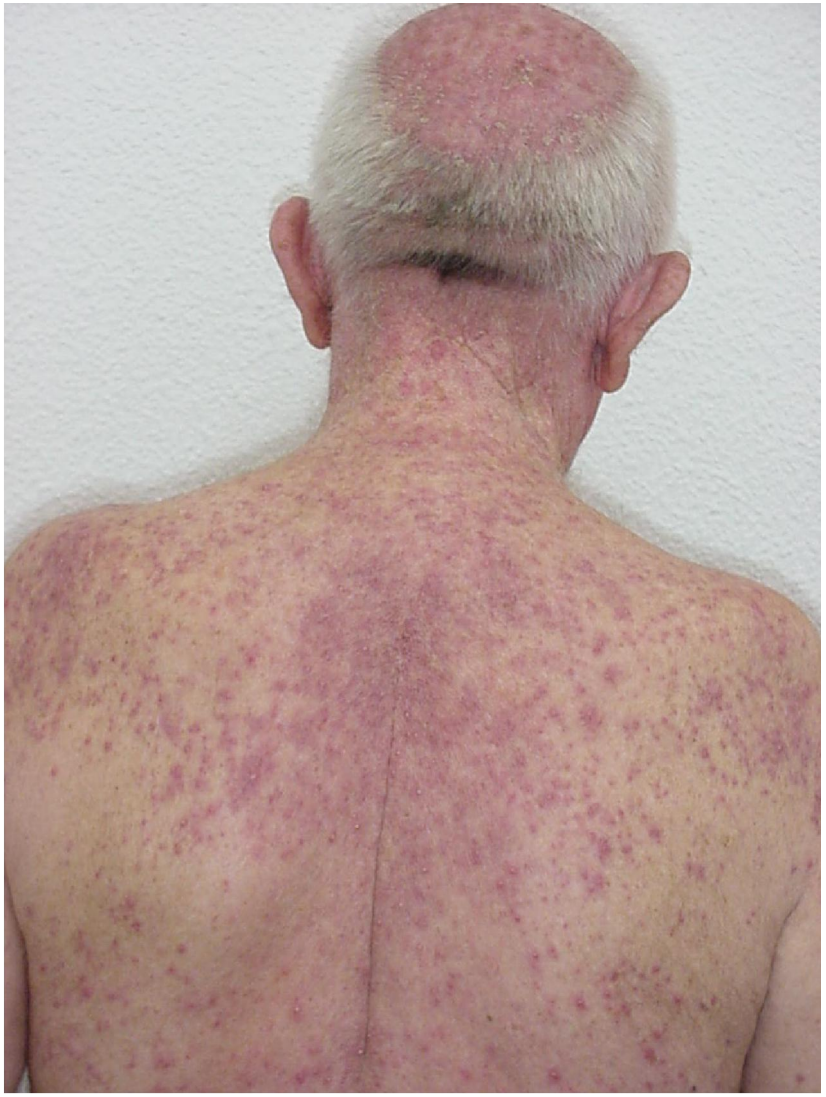
- Bloqueo EGFR →detención de maduración del folículo (de anagen a catagen) → necrosis →foliculitis secundaria
- Mismo efecto a nivel ungueal

Reaccion pápulo-pustular

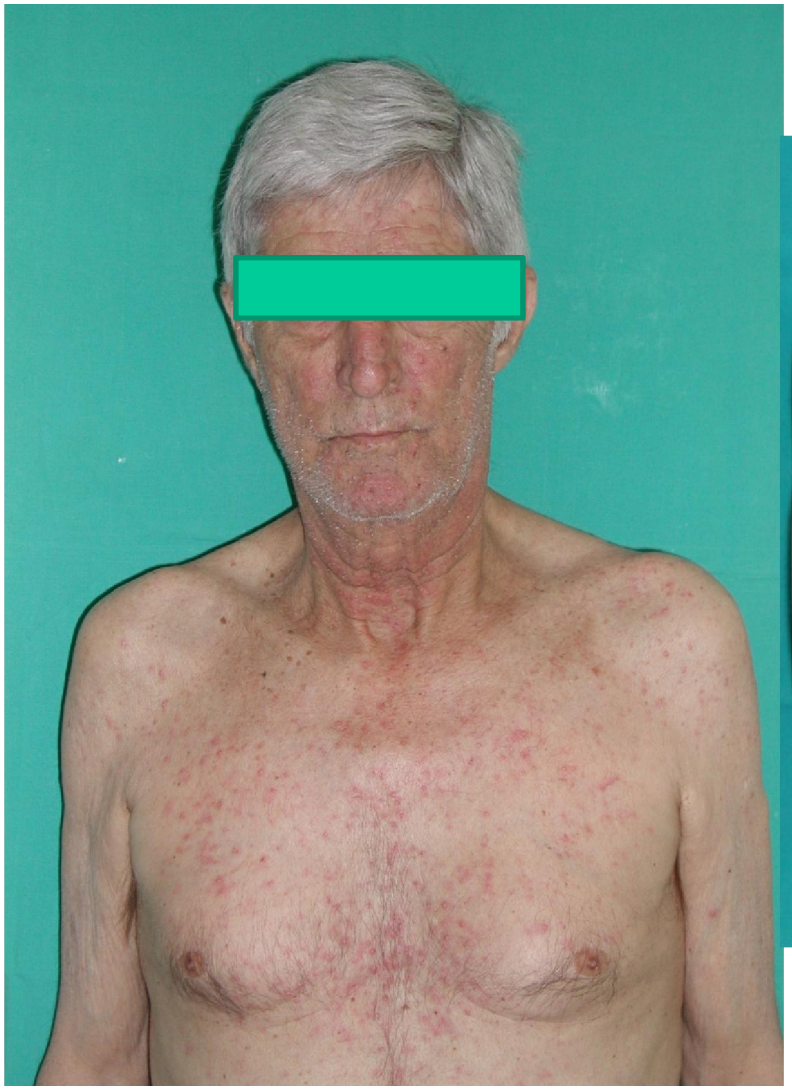
- Pápulas y pustulas sobre base eritematosa
- Presente en el 60-100% de pacientes
- Intensidad relacionada con la respuesta al tratamiento
- Inicio al 8 día tras tratamiento, con máxima intensidad a las 2-4 semanas
- Su intensidad disminuye al 4º mes
- Dosis-dependiente

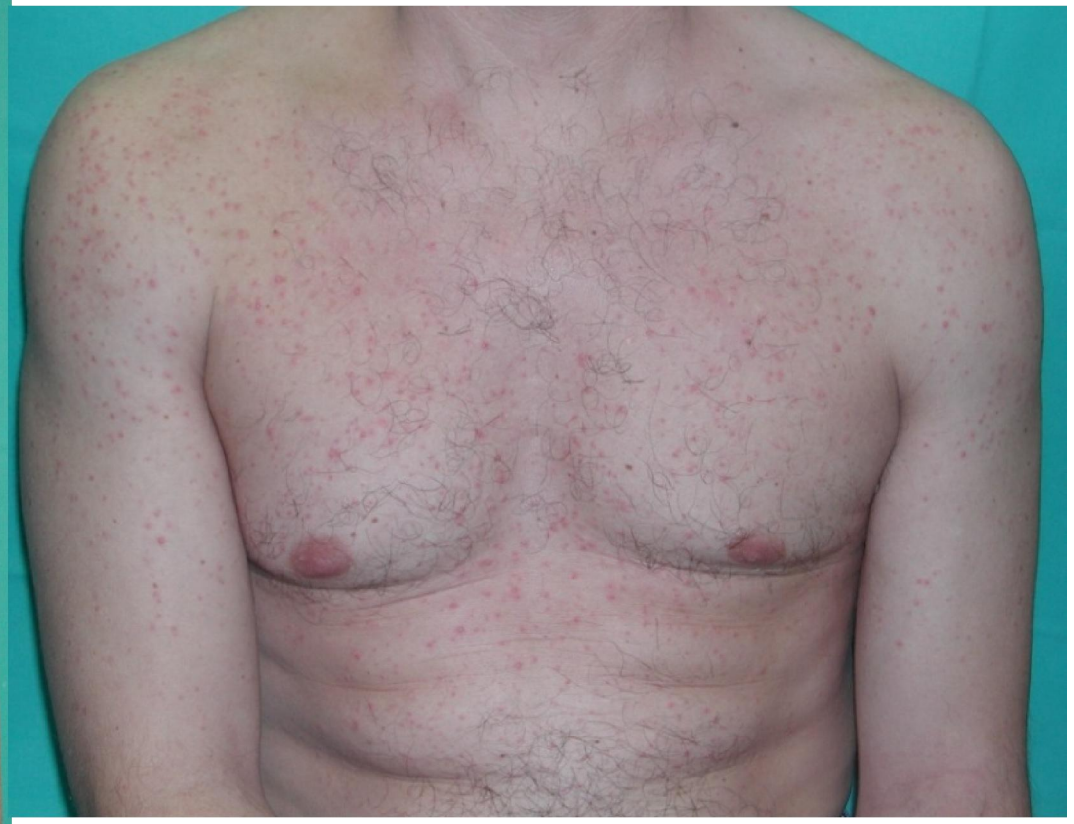




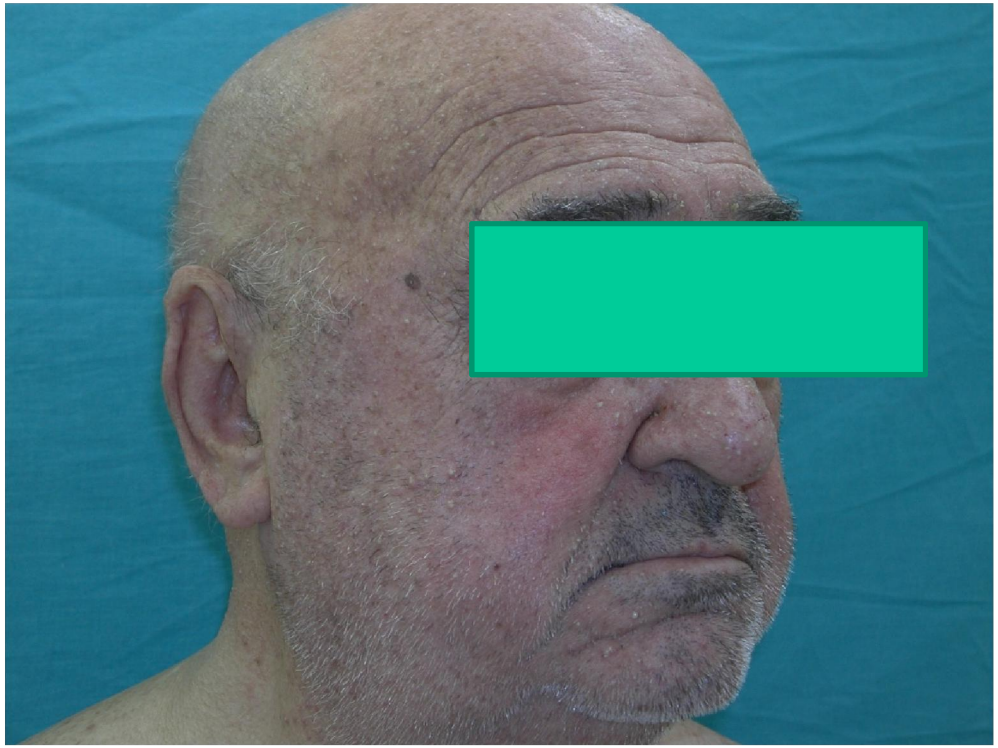


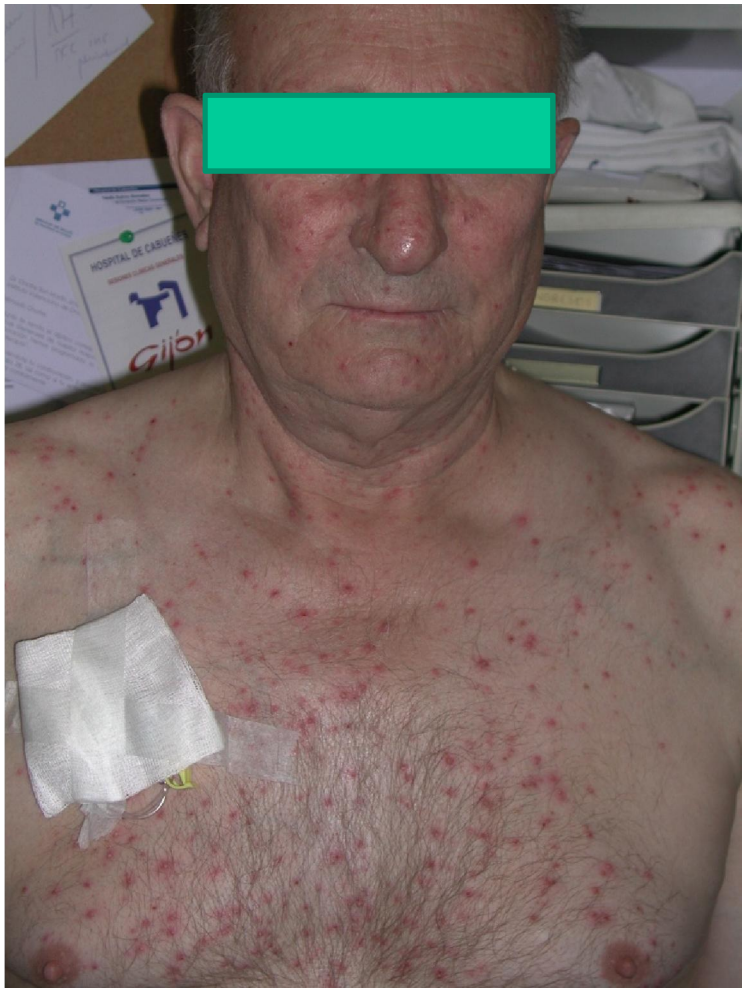
erlotinib



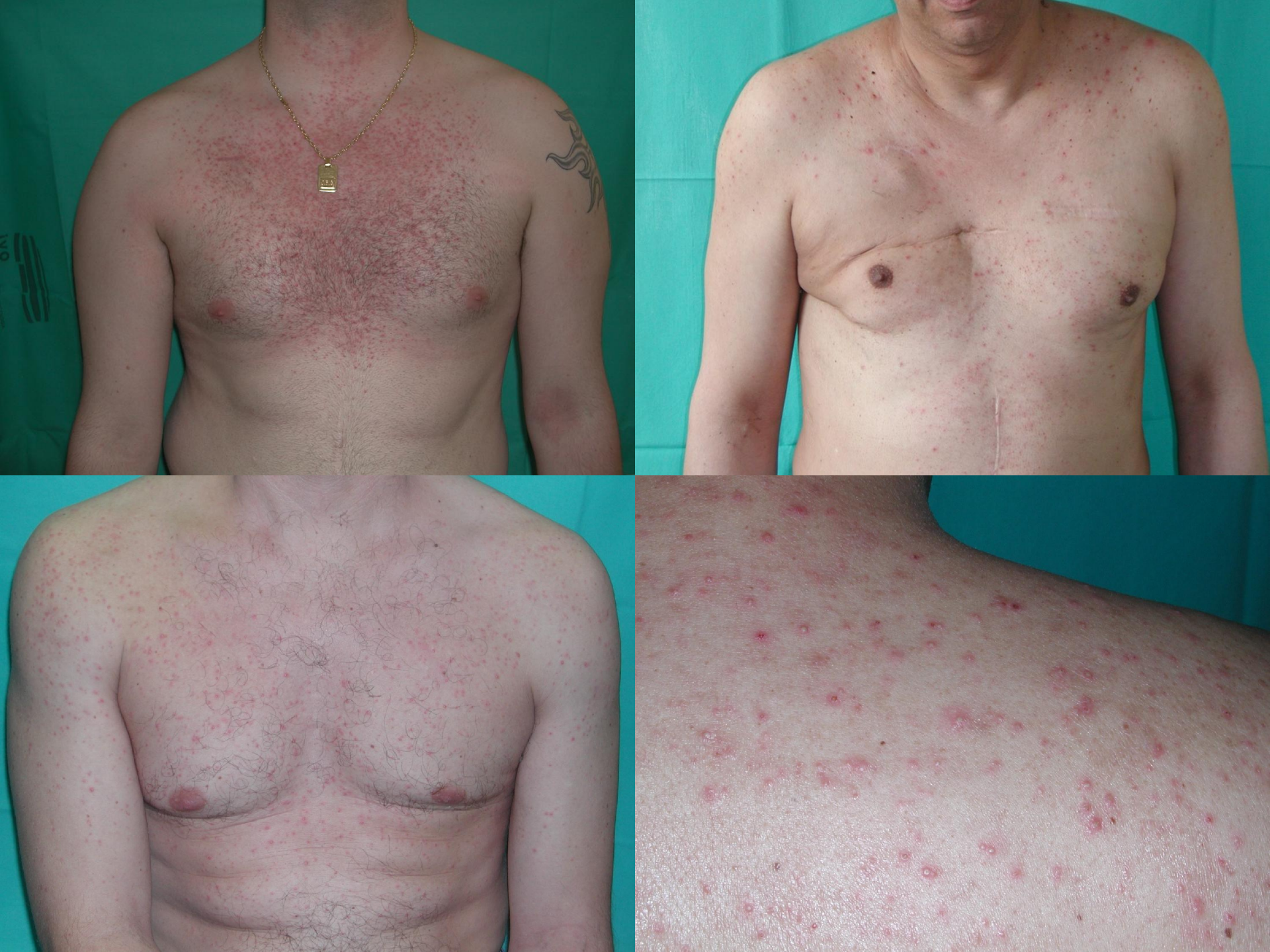


gefitinib



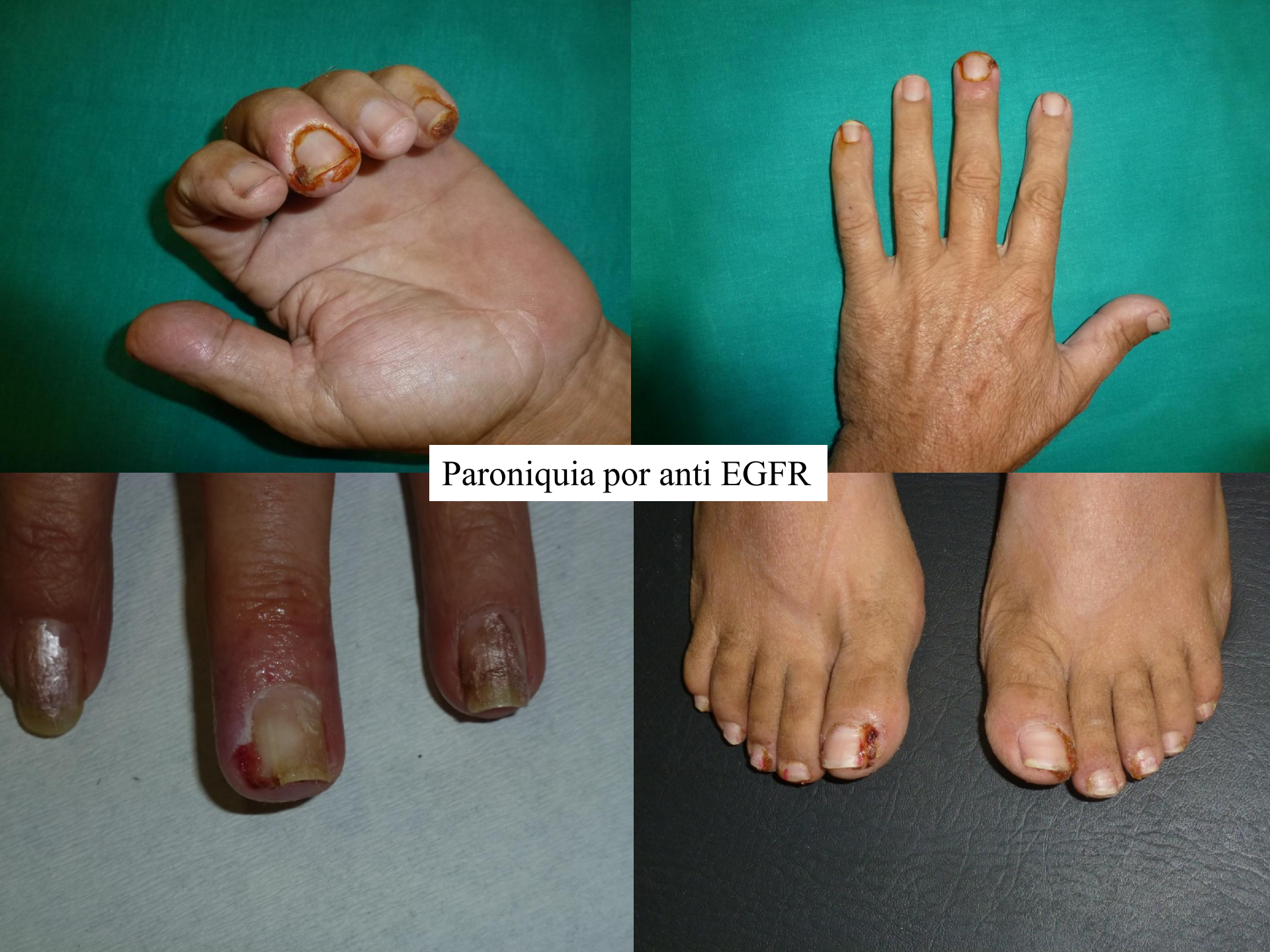


Cetuximab



Tratamiento rash pápulo-pustular

- Medidas preventivas
  - Evitar exposición solar
  - Evitar productos locales comedogénicos (pomadas, fotoproteccion grasa, etc.)
  - Evitar productos tópicos de base alcohólica (irritante)
- Medidas locales
  - Corticoides: Periodos cortos de tiempo (foliculitis esteroidea)
  - Retinoides tópicos: Cuidado con su capacidad irritante
  - Antibioticos tópicos: elegir emulsiones o geles, evitar alcohol
- Tetraciclinas (doxiciclina y minociclina)
- Isotretinoina

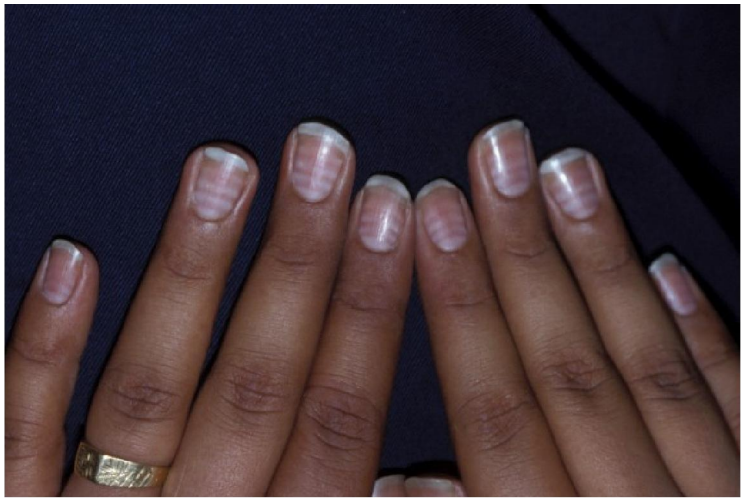


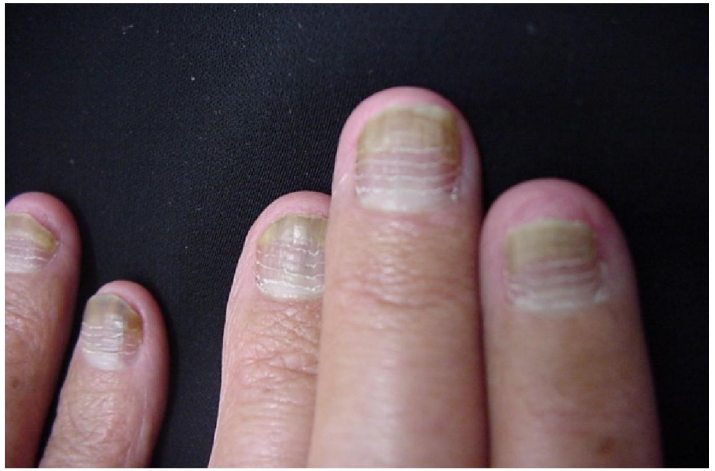
Paroniquia por anti EGFR

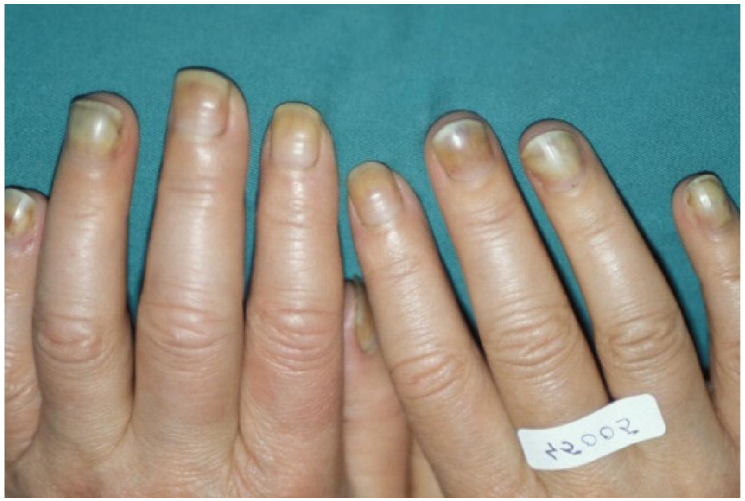
Onicolisis inducida por QT convencional

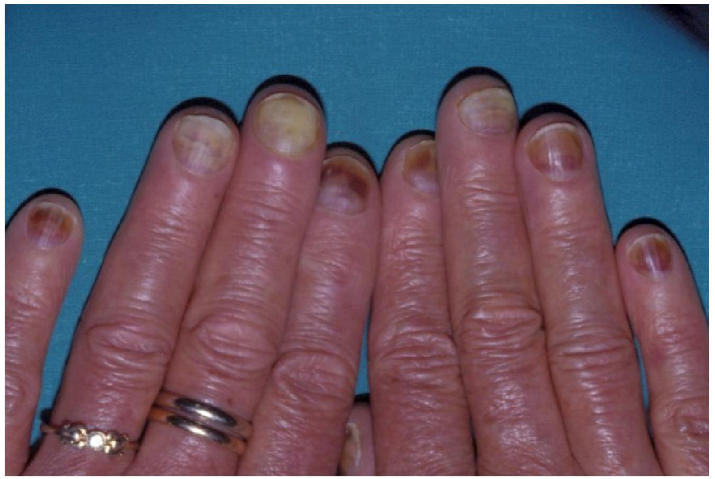
- Relación significativa con TAXANOS
- Fundamentalmente con Taxol en régimen semanal
- Incidencia entre el 2’3-2’5% de los pacientes tratados con estos agentes
- TLD en el 50% de los casos

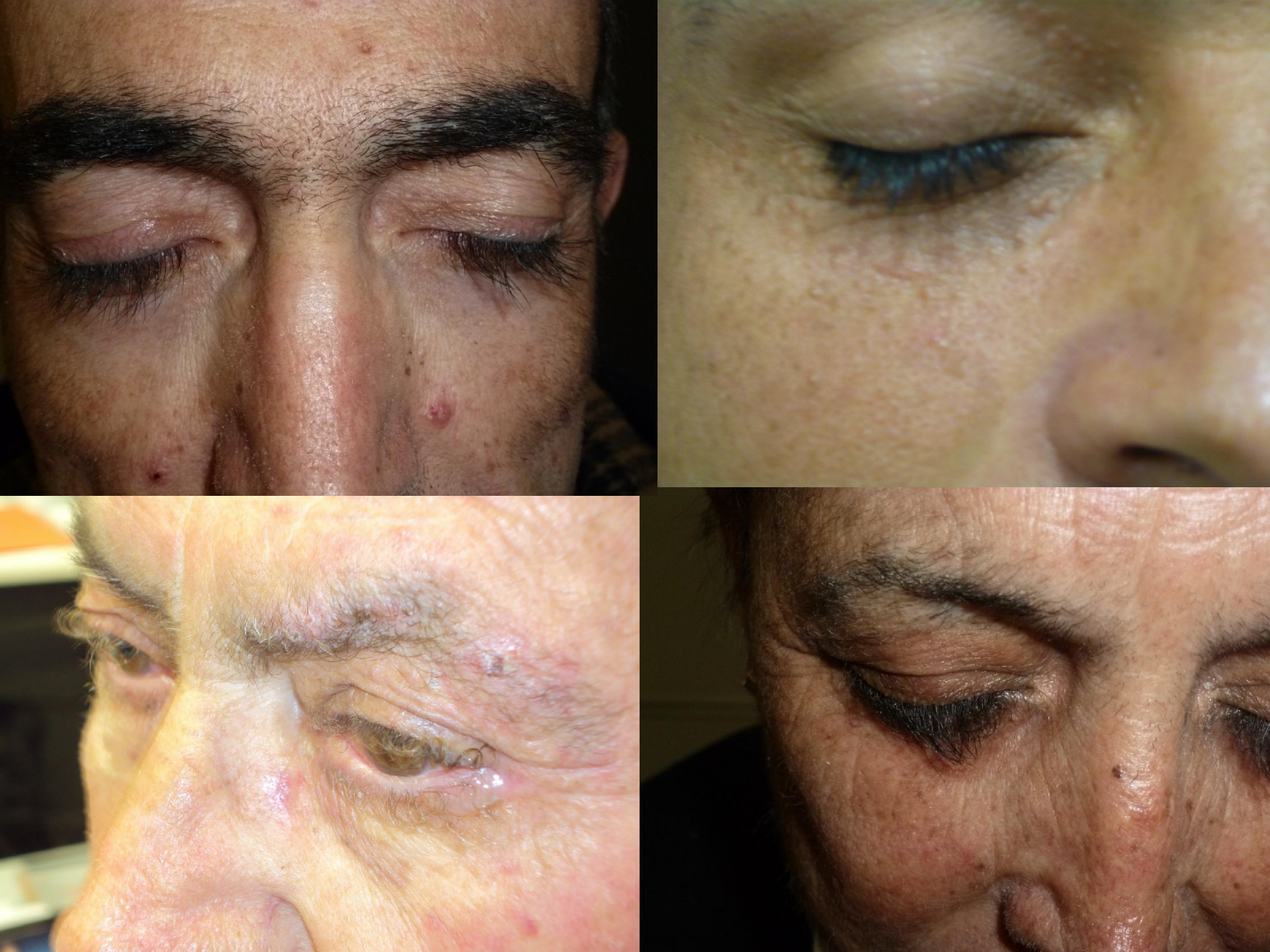
Lesiones ungueales inducidas por QT convencional









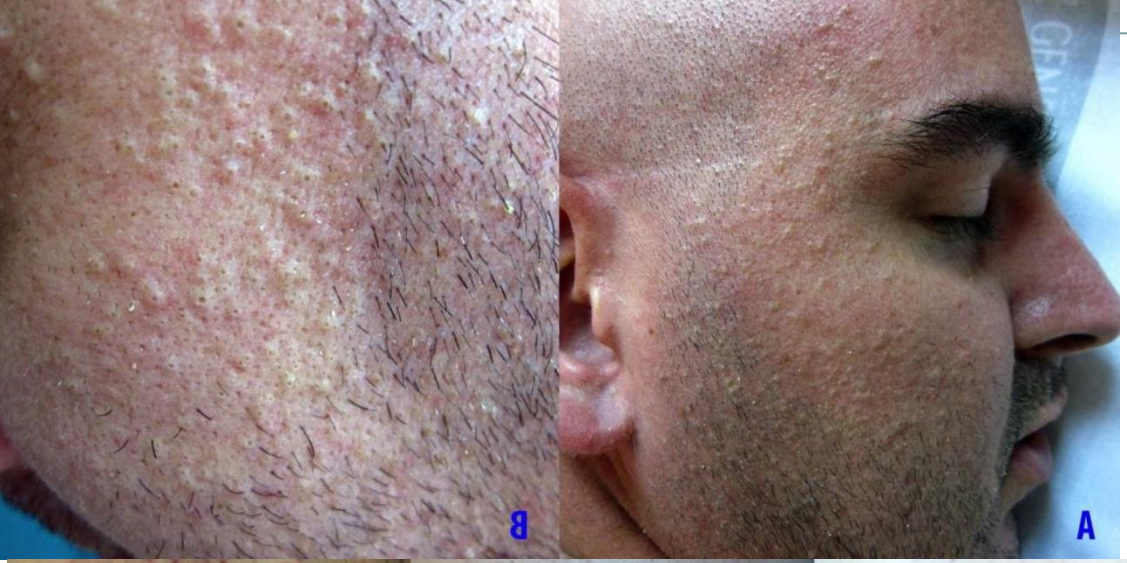


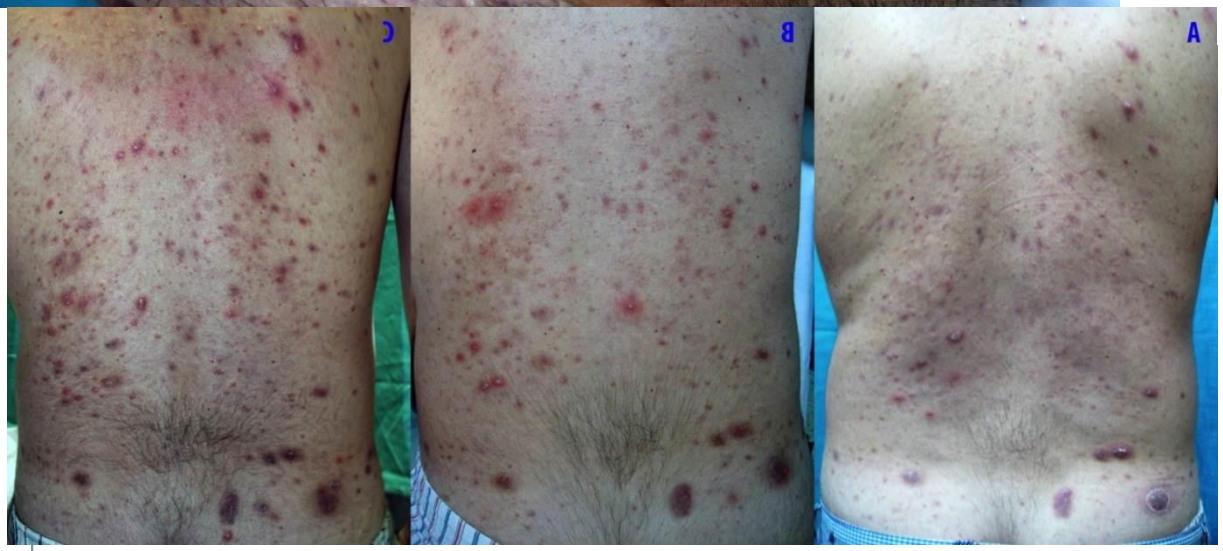
¿Cuál es el verdadero acné inducido por agentes antidiana?

VERDADERAS REACCIONES ACNEIFORMES?

- Inducidas por inhibidores de VEGFr (agentes antiangiogénicos)
- Bevazizumab: MoAb anti VEGFr
- Sorafenib: Multikinasa inh C-RAF, VEGFr and PDGFB
- Dovitinib: Multikinasa inh FGFr, VEGFr
- Pazopanib: inh VEGFr

- Estos agentes inducen hiperplasia sebácea, comedones, y finalmente acné nodular





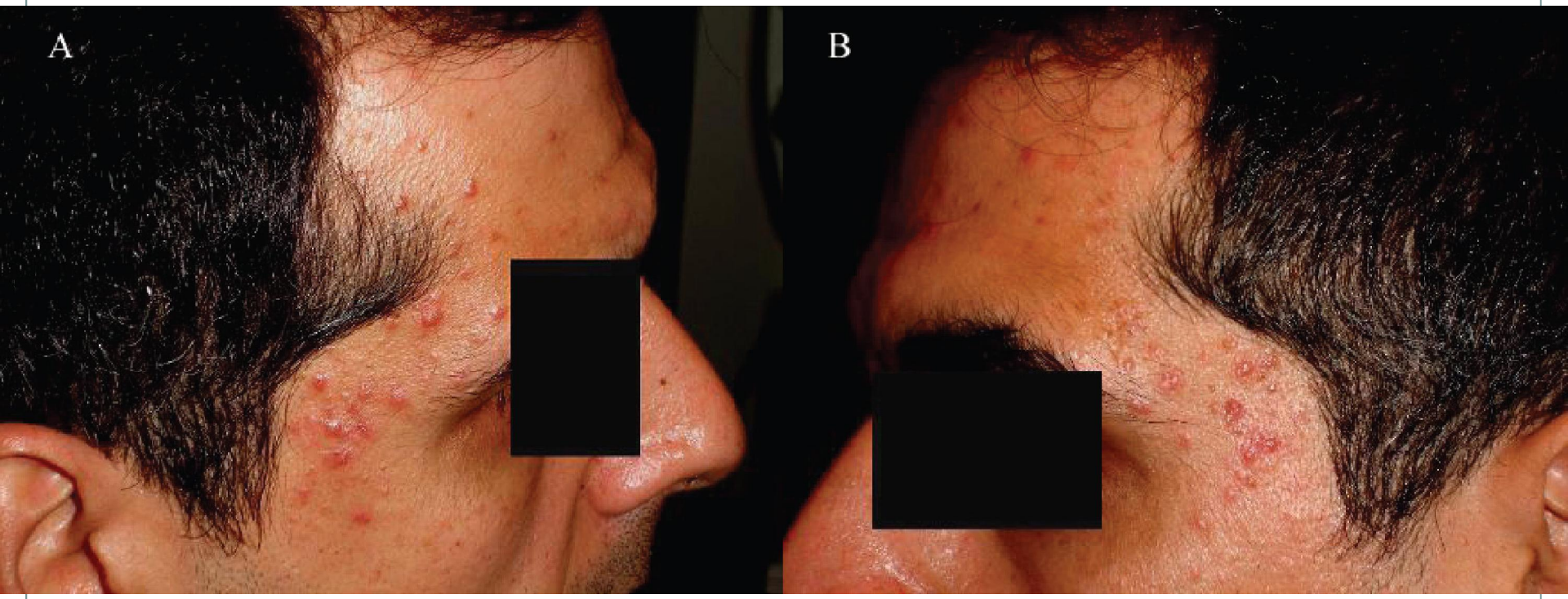
Follicular acneiform eruption induced by bevacizumab

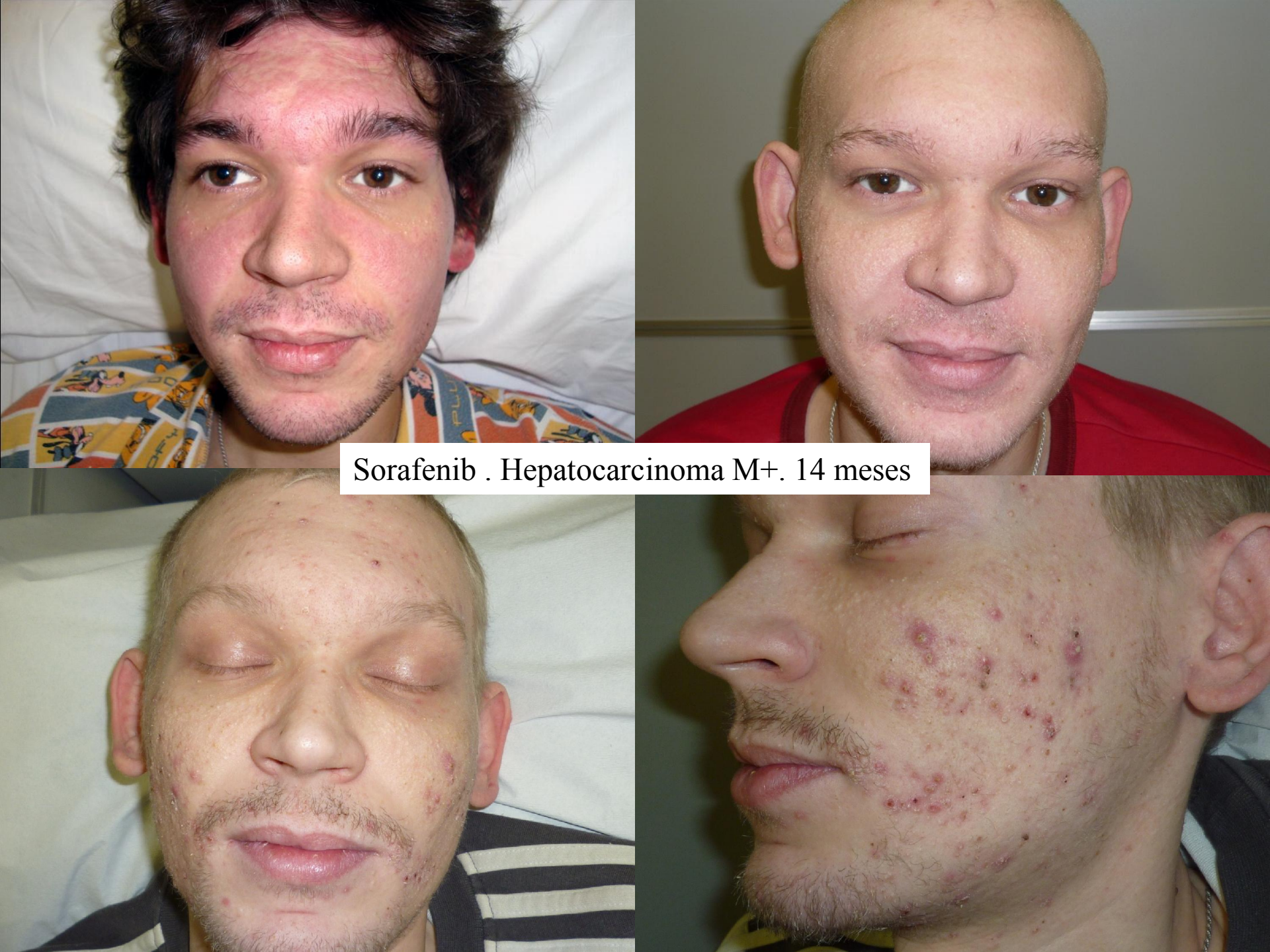
Gavrilova M.
Dermatology Online Journal 2012; 18: 15

Dermatology Online Journal

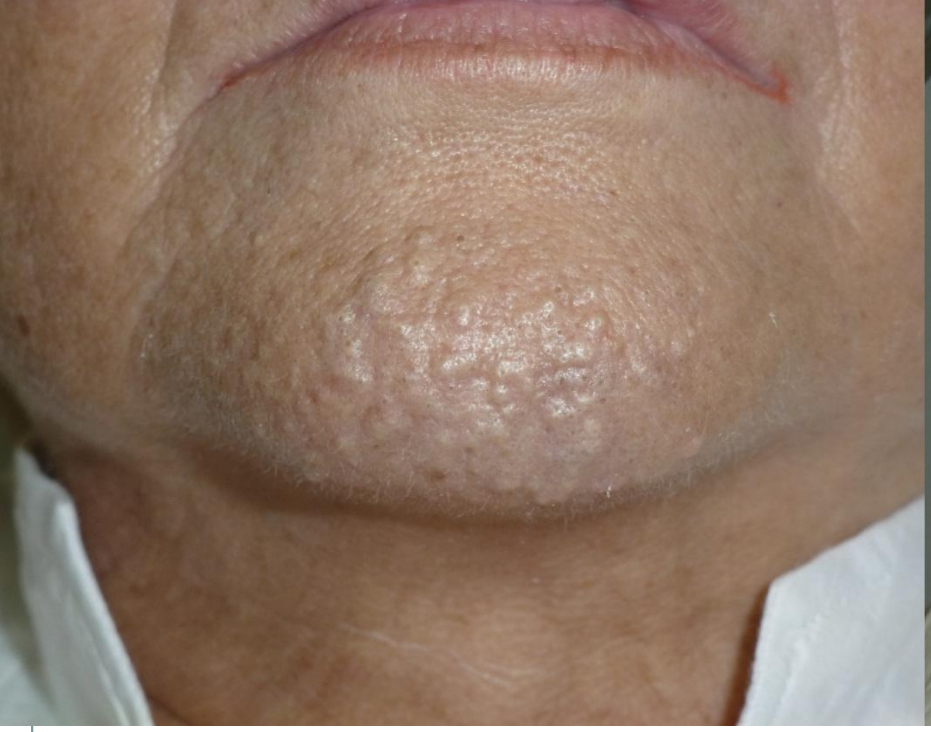
Occasional reports of acne induced by bevacizumab and sorafenib

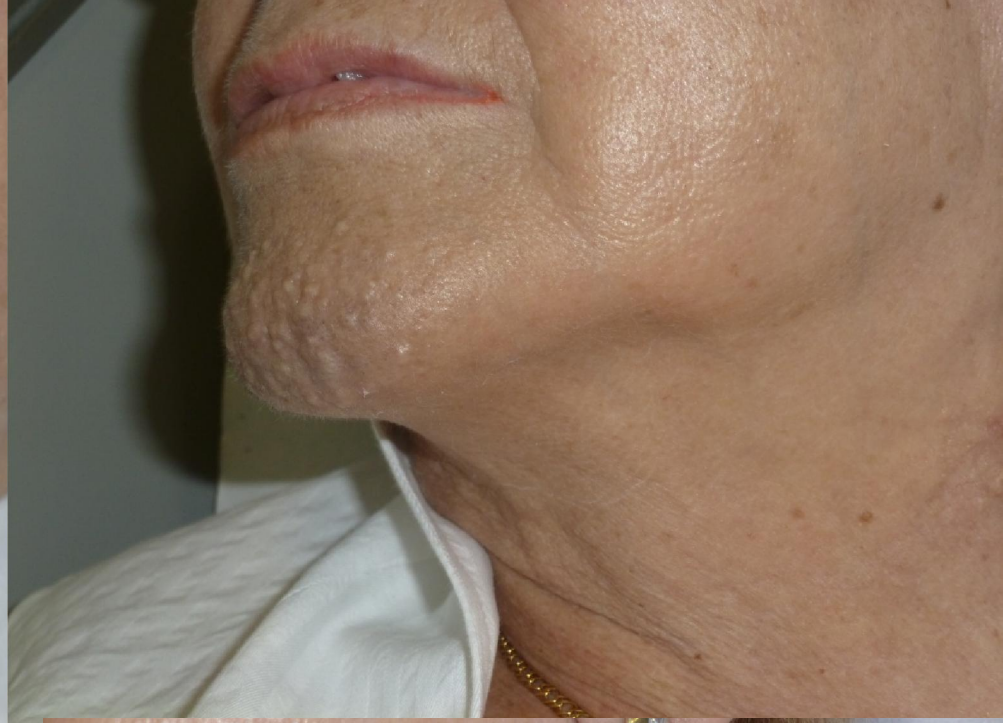
Skin rash associated with intravitreal bevacizumab in a patient with macular choroidal neovascularization



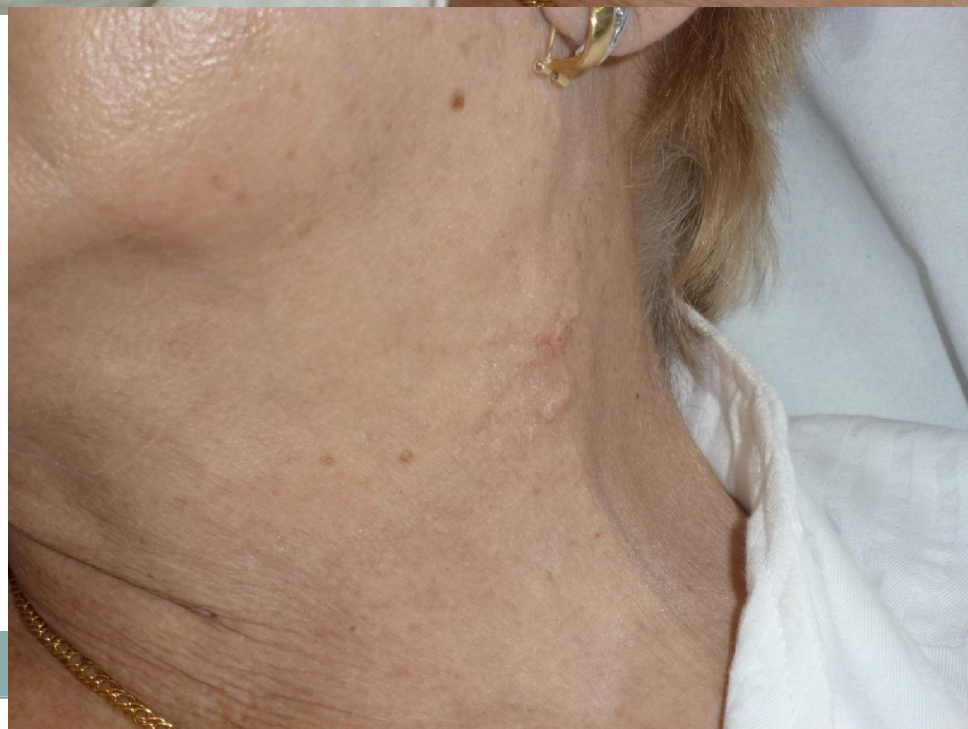


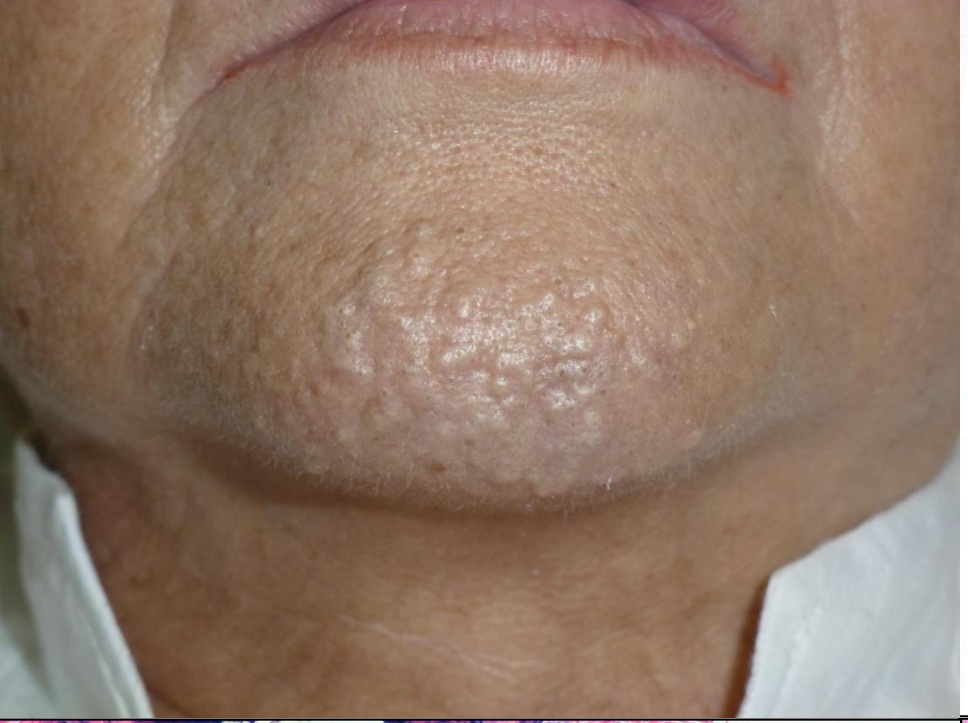
Sorafenib . Hepatocarcinoma M+. 14 meses

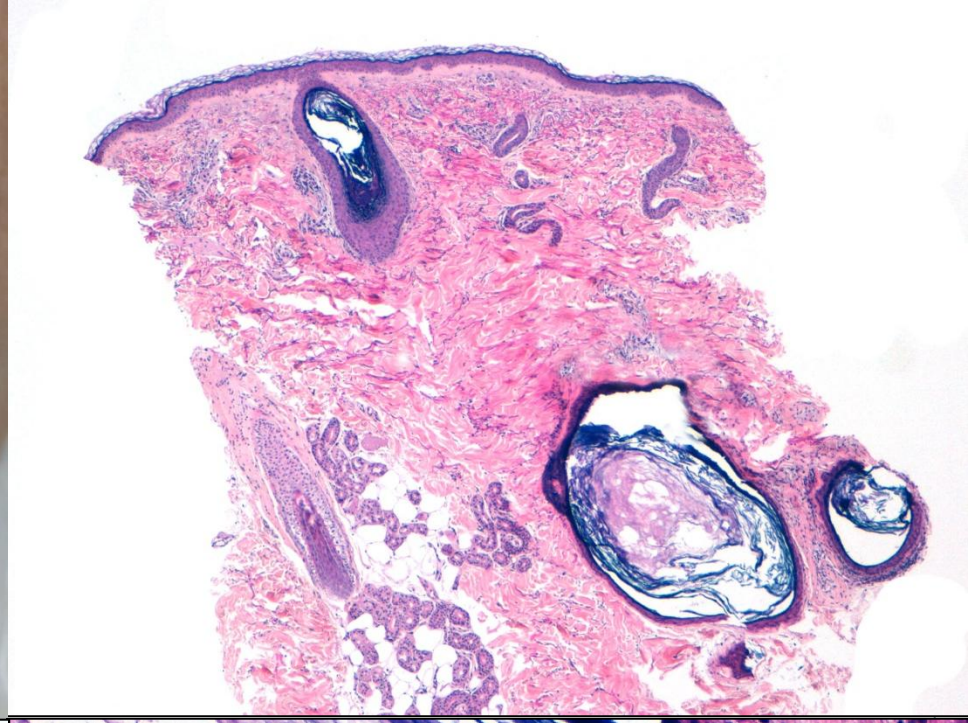


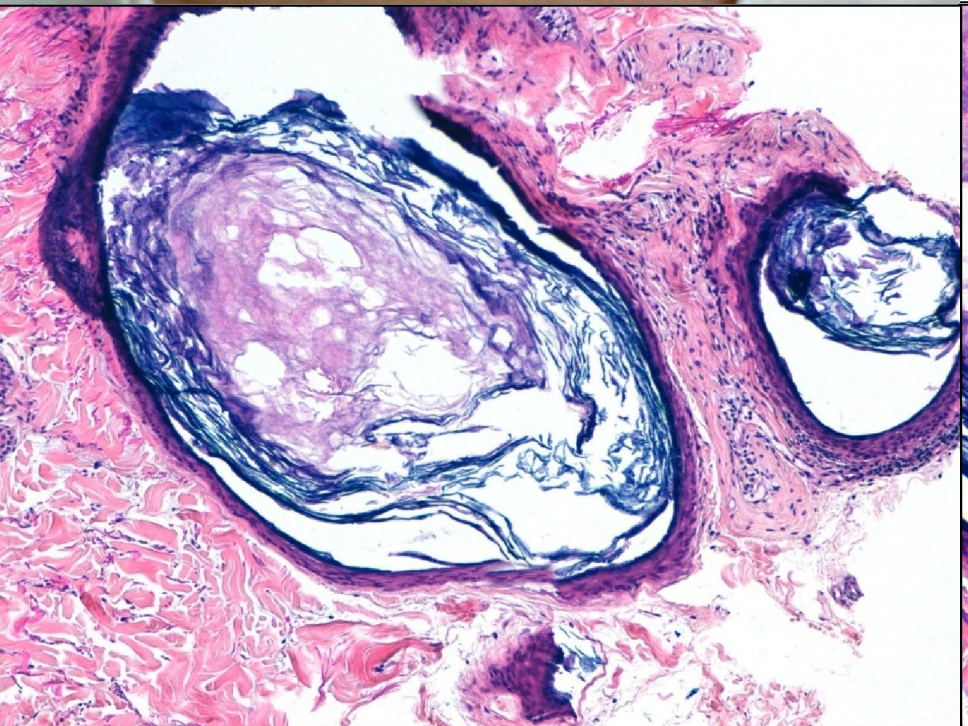


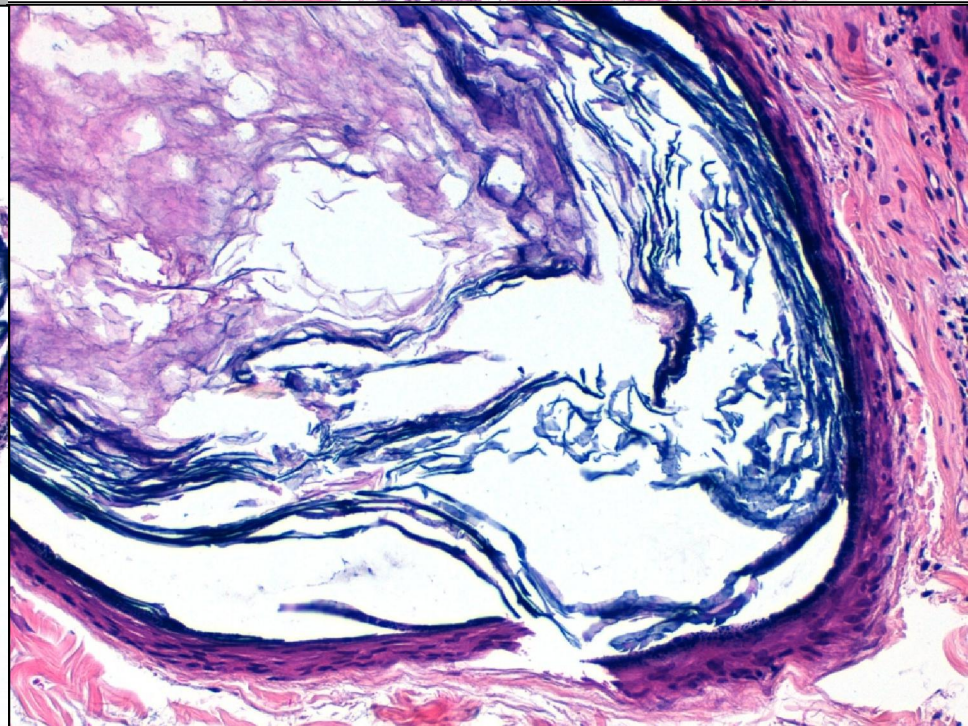
63 años, mujer
Cancer suprarrenal M+
Dovitinib monoterapia
Buena respuesta
Primer mes de tratamiento

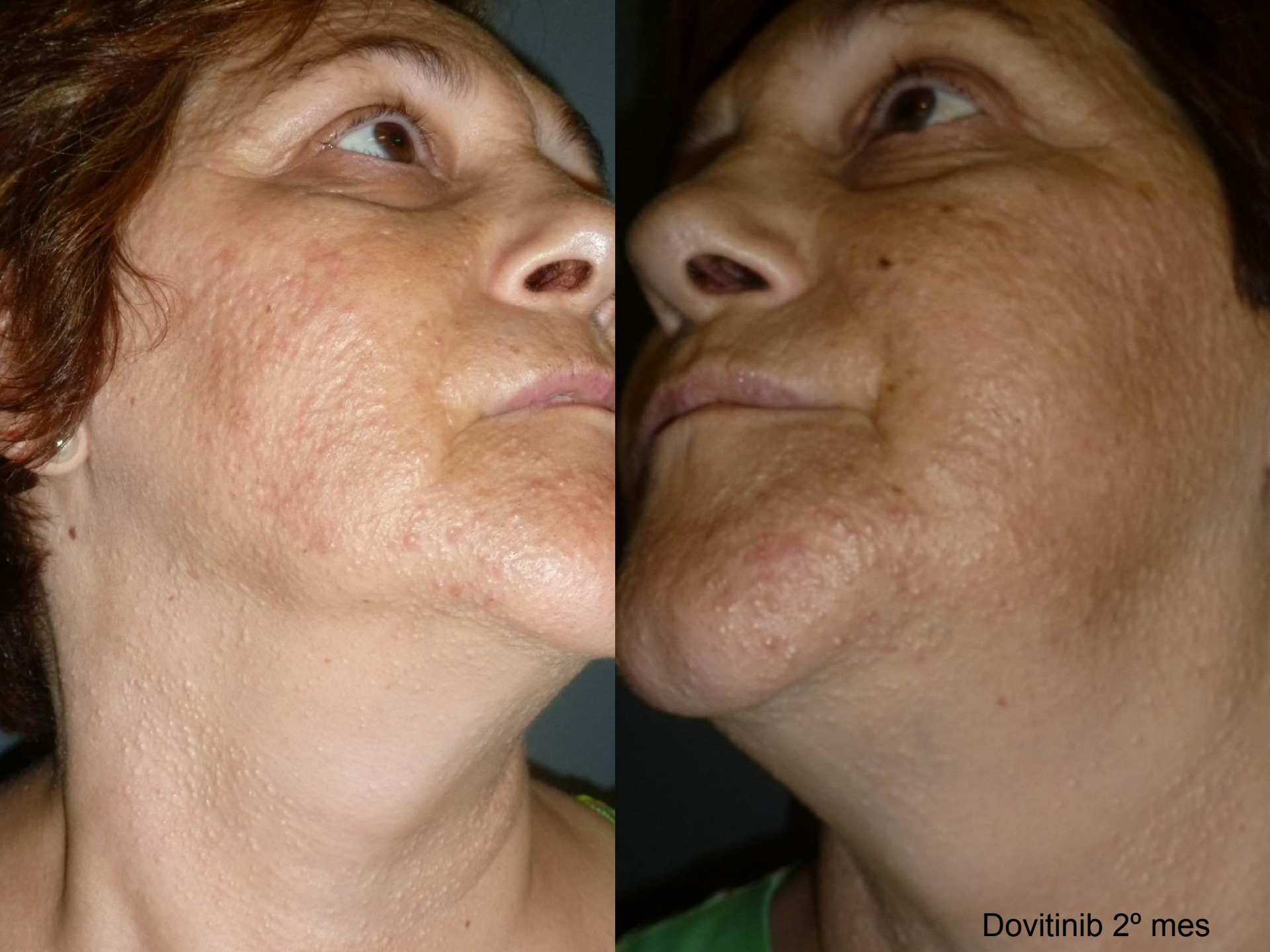


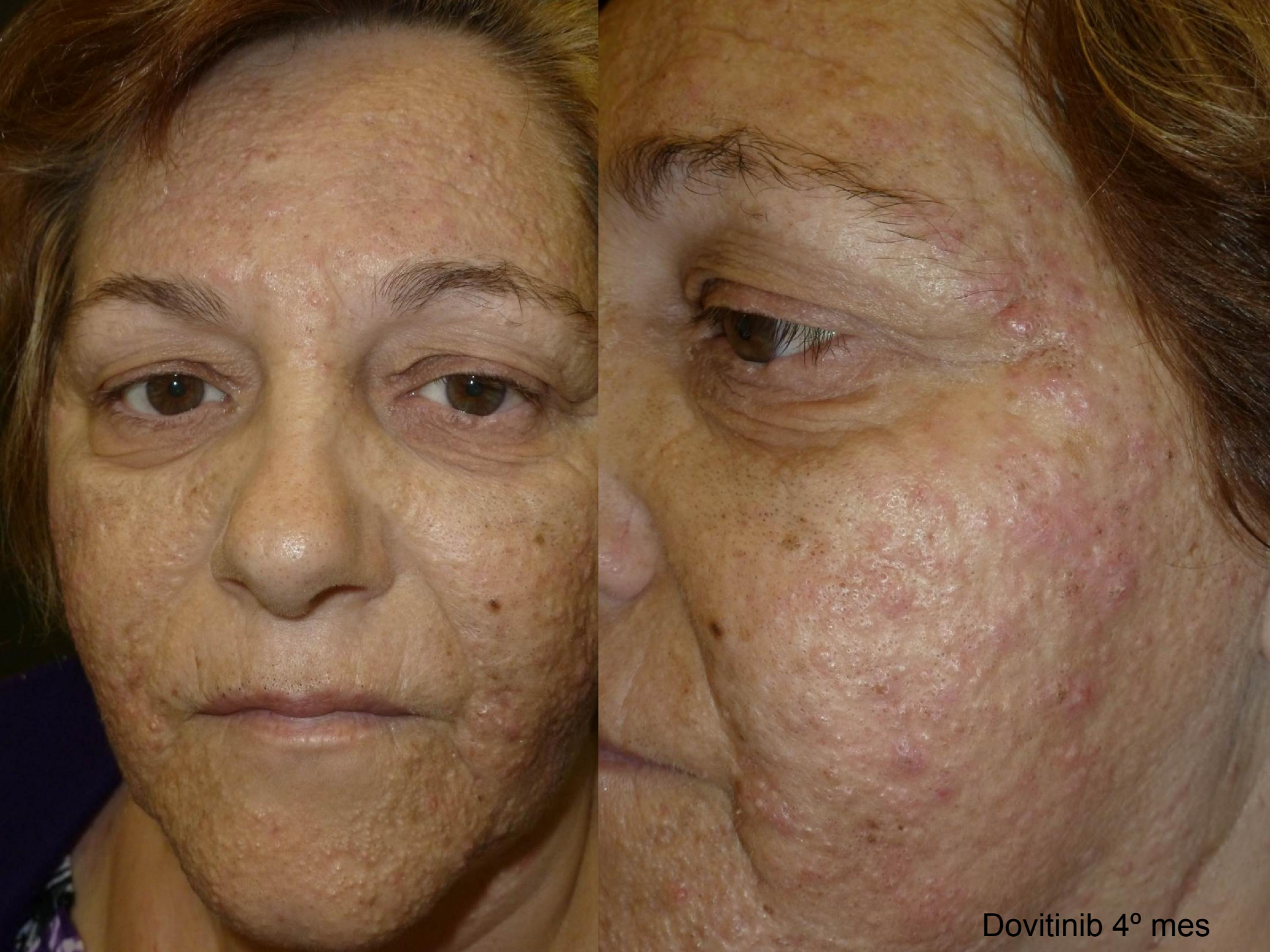









Dovitinib 2º mes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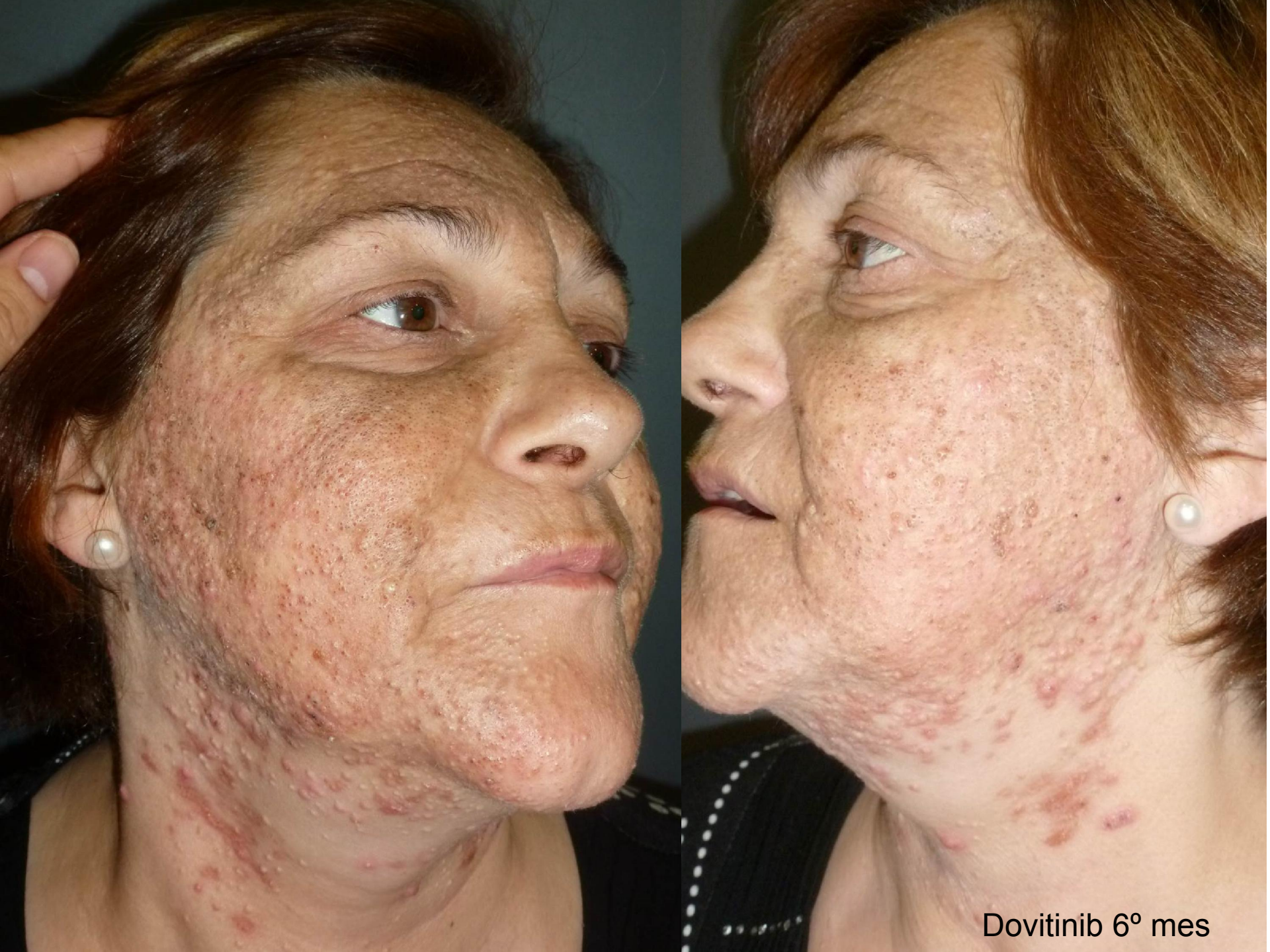
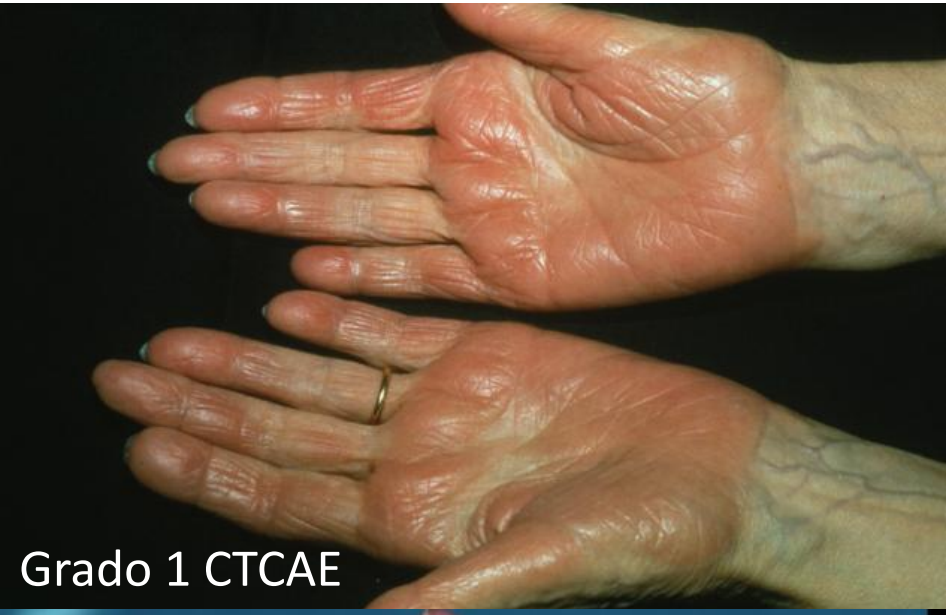
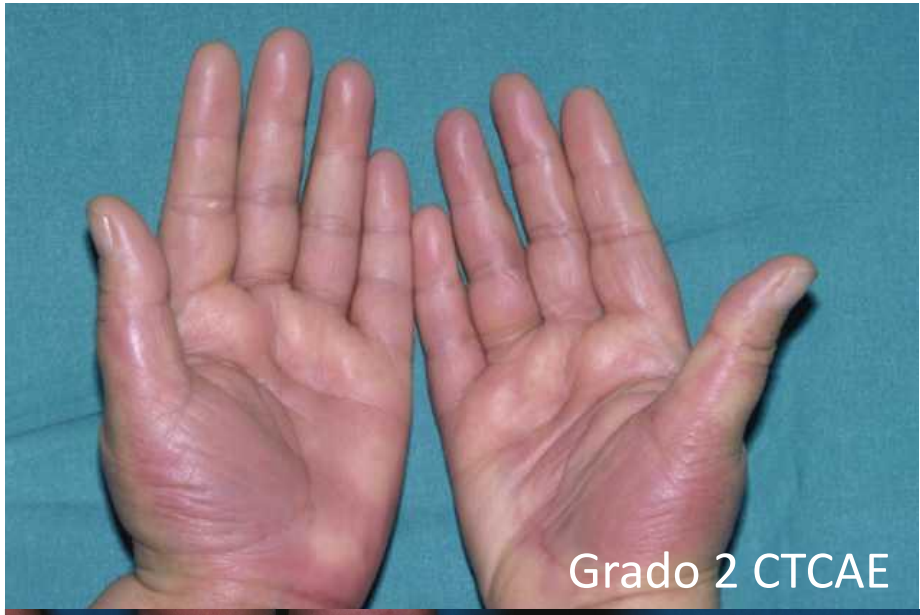

Dovitinib 6º mes

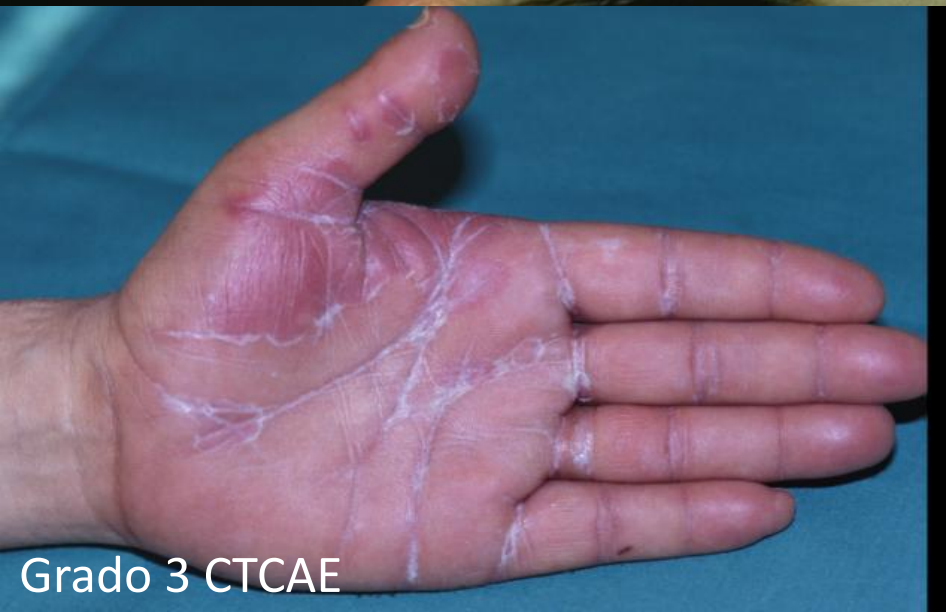
ACNE NODULAR INDUCIDO POR inhibidores VEGFr

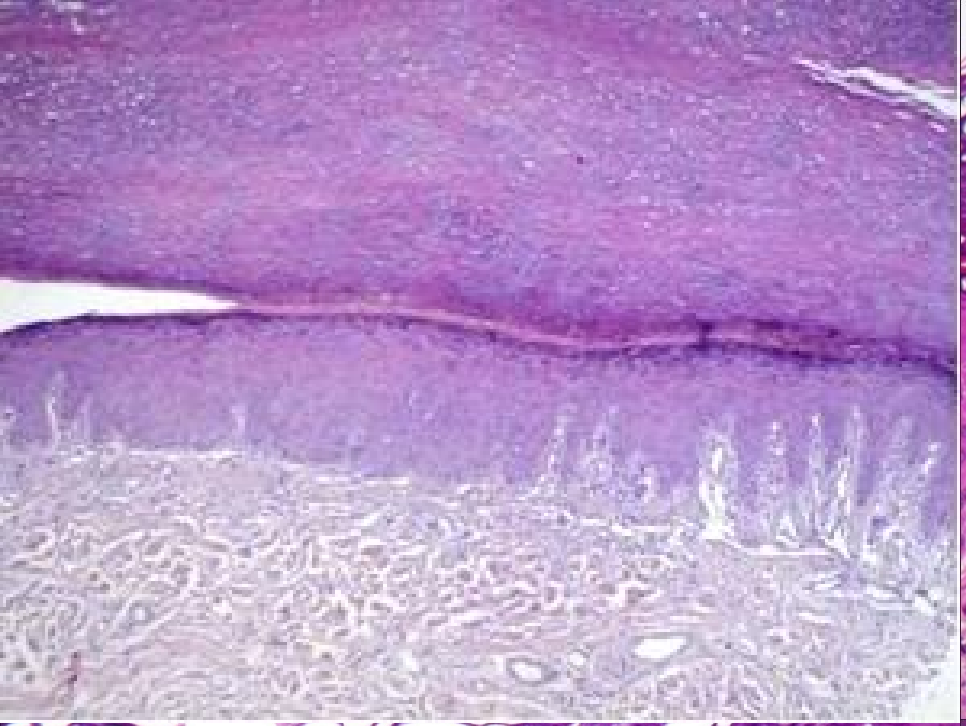
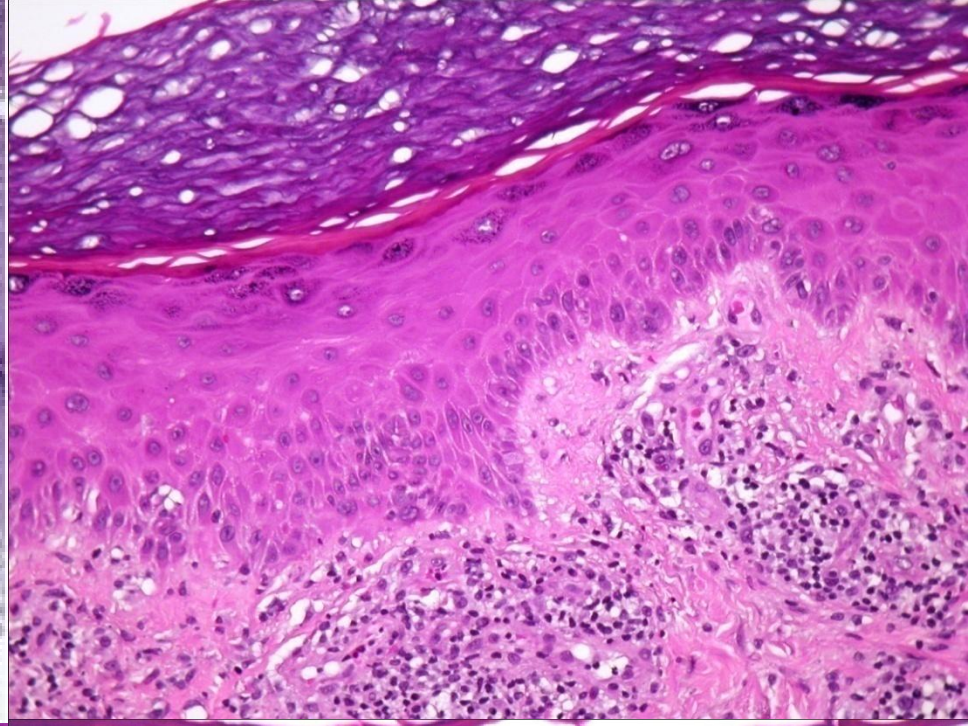
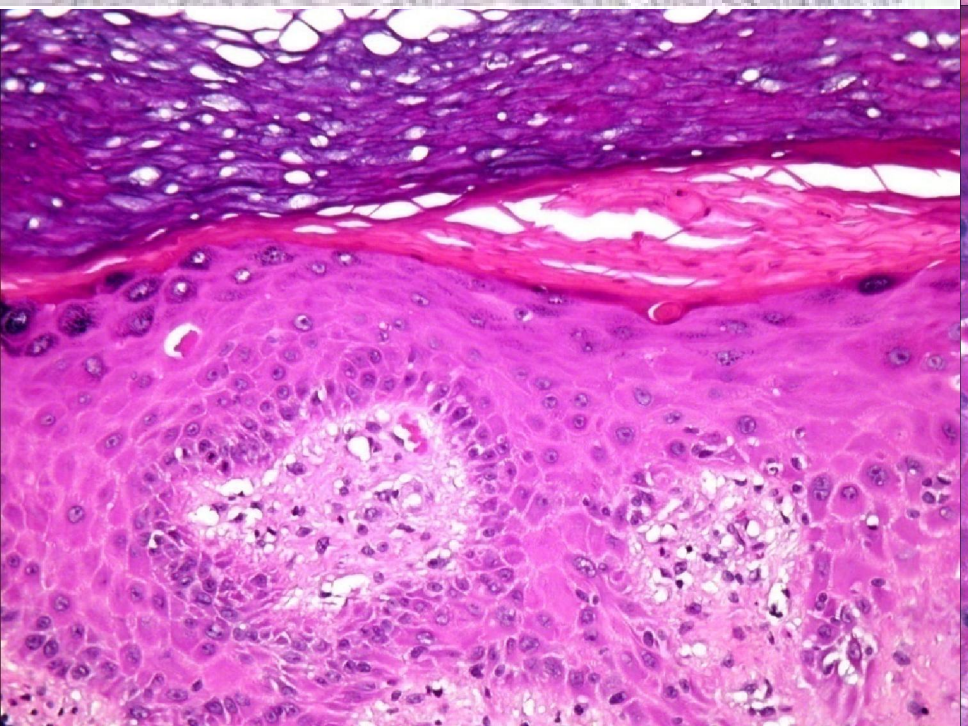
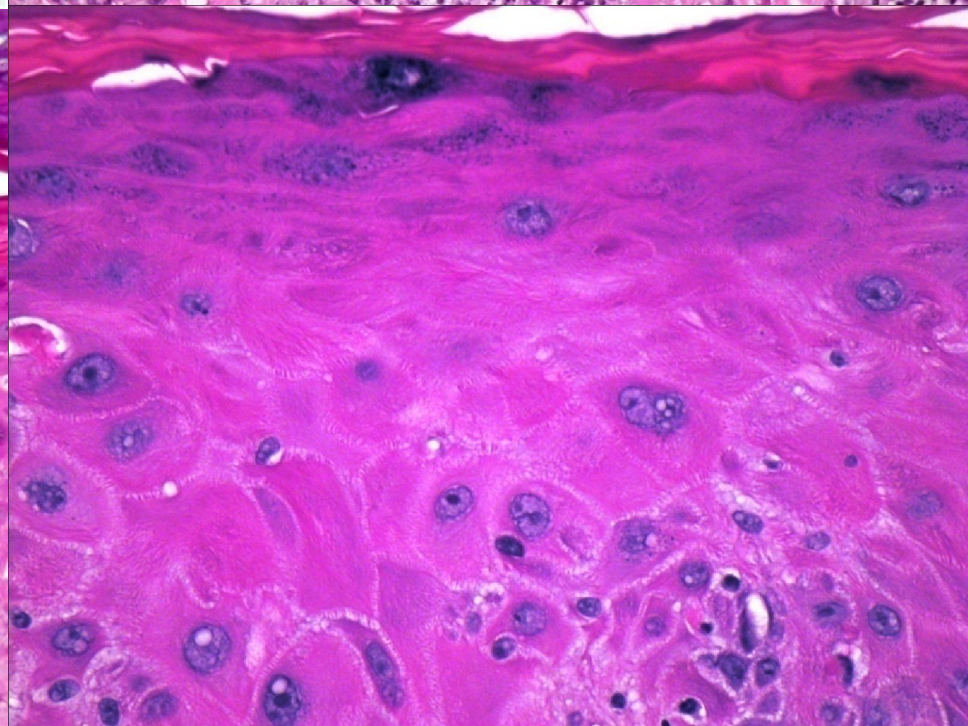
- Bevazizumab, sorafenib, dovitinib, pazopanib
- Agrandamiento progresivo de glándulas sebáceas
- Desarrollo de tapones foliculares, comedones y quistes
- Finalmente evolucion a acne nodular

Eritema Acral inducido por quimioterapia







Actas Dermosifiliogr. 2008;99:281-90

ORIGINAL ARTICLES

Chemotherapy-Induced Acral Erythema: A Clinical and Histopathologic Study of 44 Cases

L. Hueso, O. Sanmartín, E. Nagore, R. Botella-Estrada, C. Requena, B. Llombart, C. Serra-Guillén, A. Alfaro-Rubio, and C. Guillén

Servicio de Dermatología, Instituto Valenciano de Oncología, Valencia, Spain

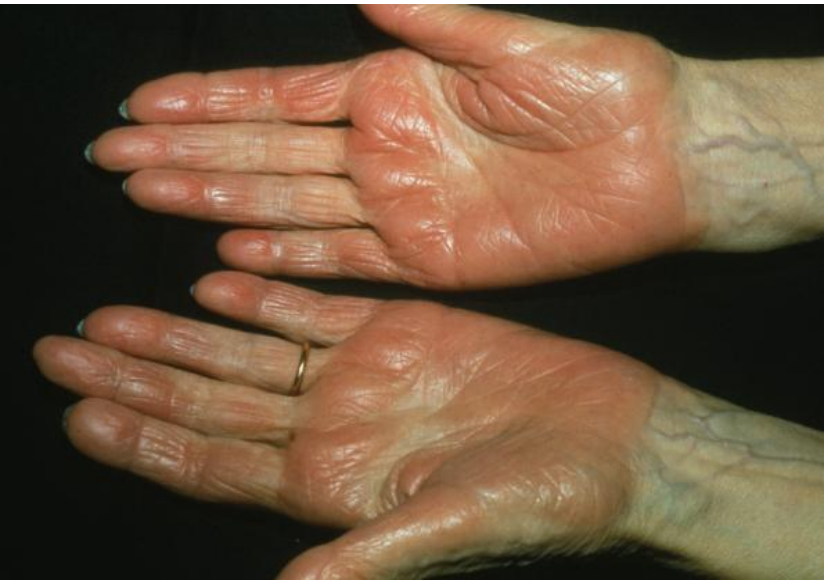


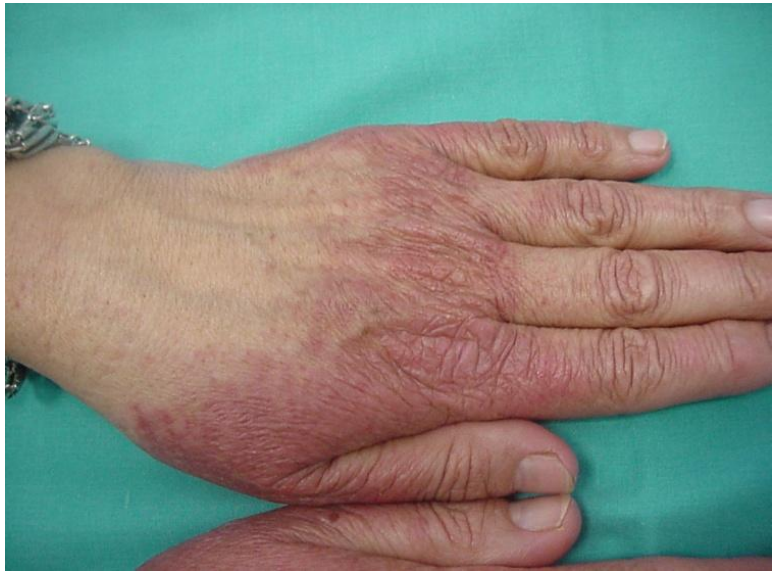
Table 2. Cases of Acral Erythema in the Present Series

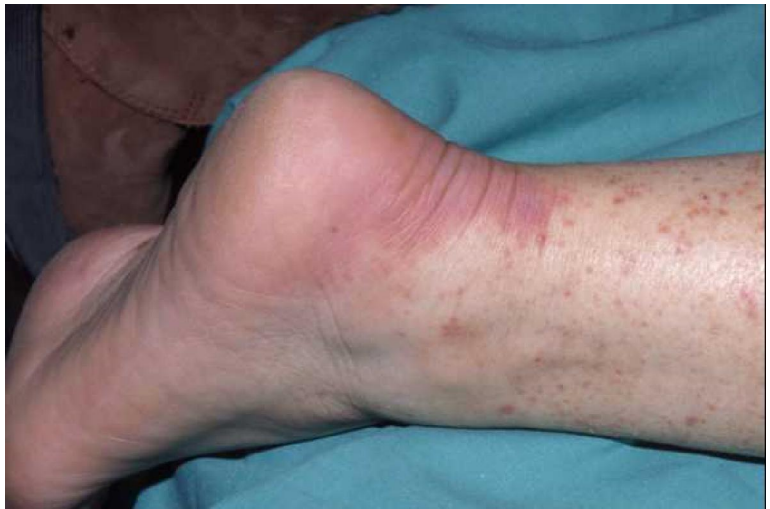
Drug	Epidemiology				Severity			Site of Lesions	
	No. of Patients	%	Patients Receiving Treatment, No.	Occurrence, %	G1[1]	G2[1]	G3[1]	Palms/soles	Palms/soles and elsewhere
5-fluoracil CI	10	22.7	46	21.7	2	4	4	10	0
5-fluoracil bolus	6	13.6	786	0.7	1	4	1	6	0
Doxorubicin	3	6.8	649	0.4	0	2	1	3	0
L-doxorubicin	5	11.3	12	41.6	0	3	2	3	2
Paclitaxel	2	4.5	127	1.5	0	2	0	0	2
Docetaxel	6	13.6	156	3.2	0	3	3	5	1
Methotrexate	3	6.8	323	0.9	1	2	0	3	0
Vinorelbine	4	9	126	3.1	1	2	1	4	0
Gemcitabine	2	4.5	31	6.4	0	1	1	2	0
Cytarabine	1	2.2	9	11	0	1	0	1	0
Cyclophosphamide	2	4.5	991	0.2	2	0	0	2	0
Total	**44**				**7**	**24**	**13**	**37**	**5**

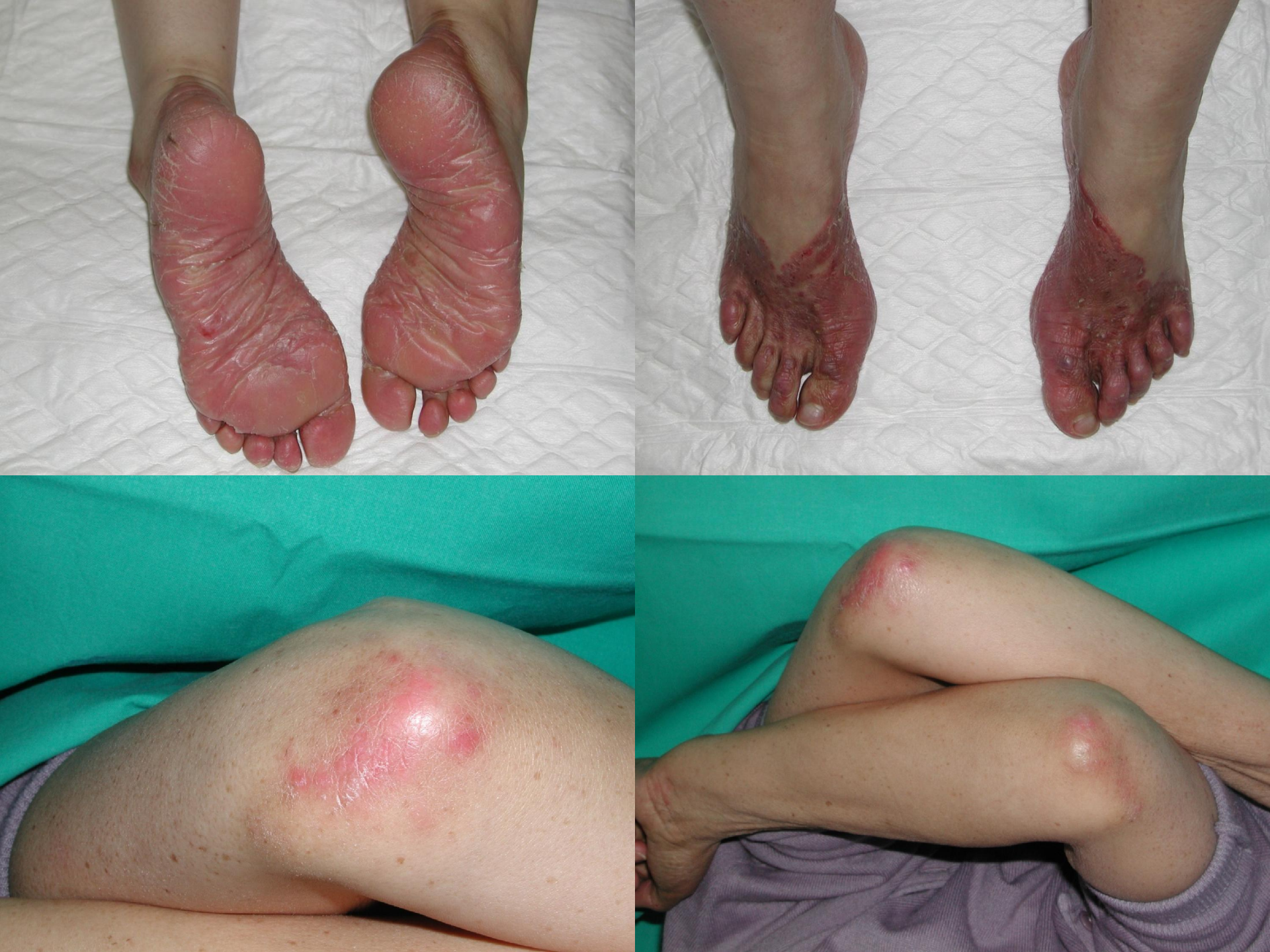
Eritema acral inducido por quimioterapia

Variedades clínicas

- Variedad de localización extrapalmoplantar (dorso manos y talones)
- Relacionada significativamente con TAXANOS Y DOXORUBICINA-L



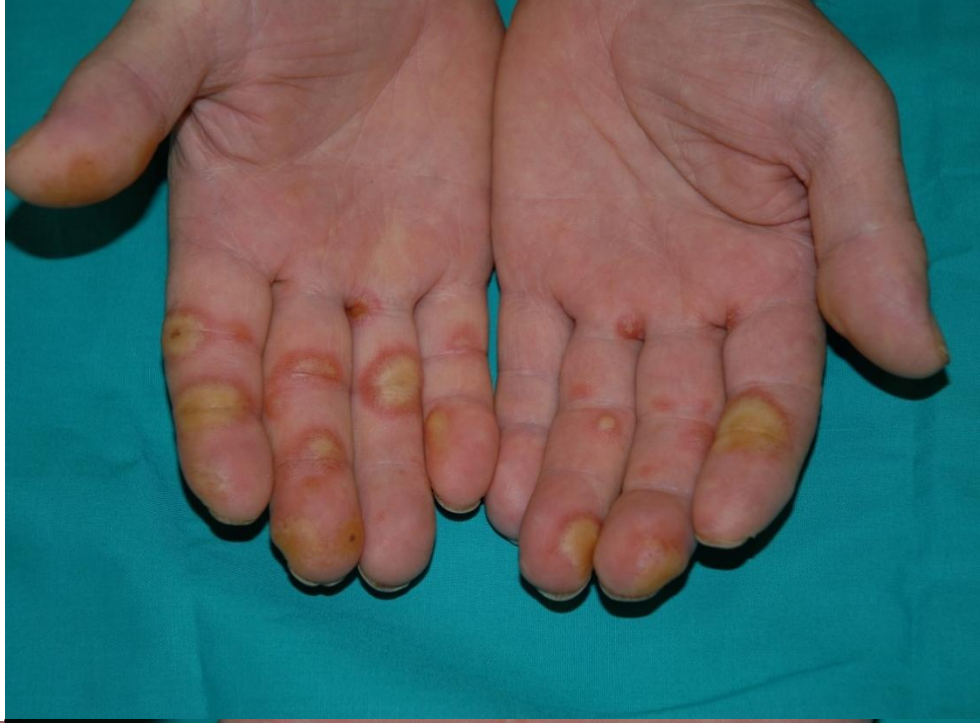


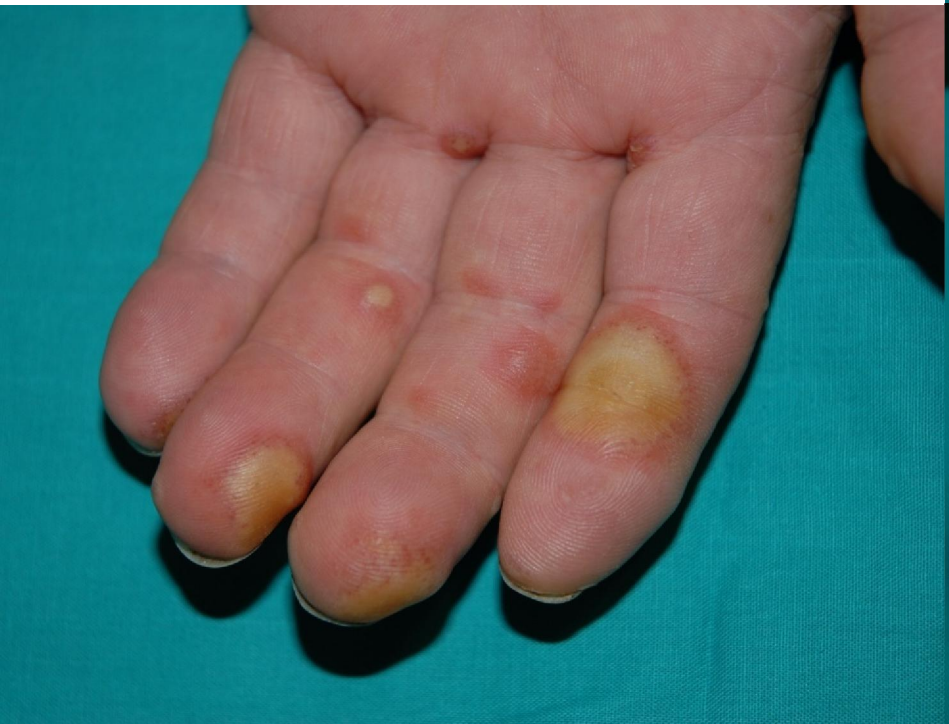


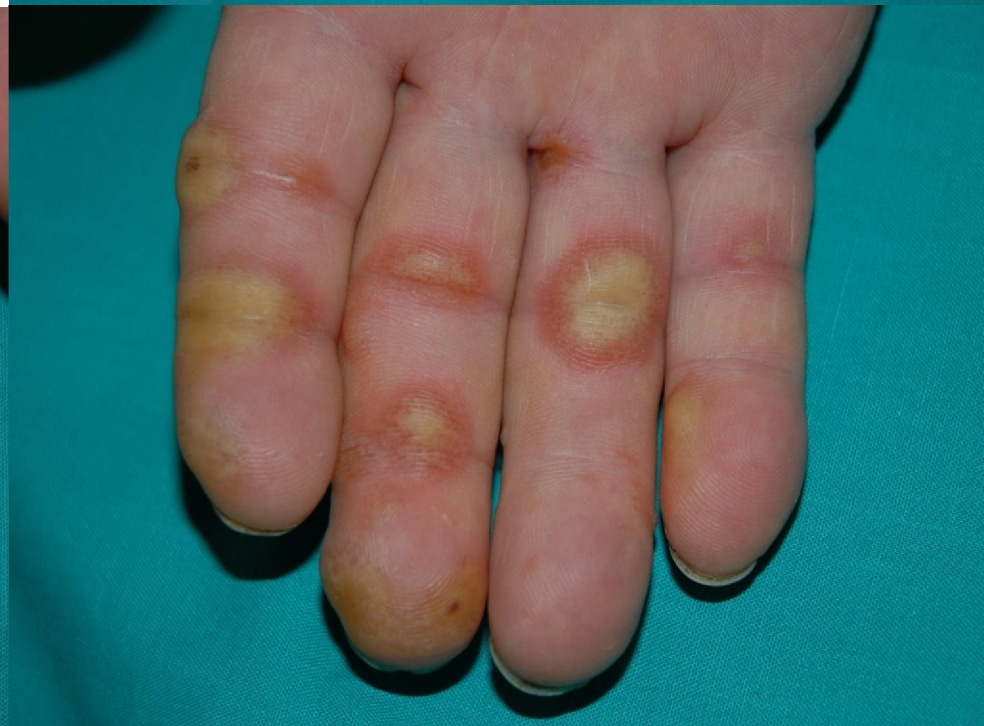
SINDROME PIE-MANO POR INHIBIDORES MULTIKINASA

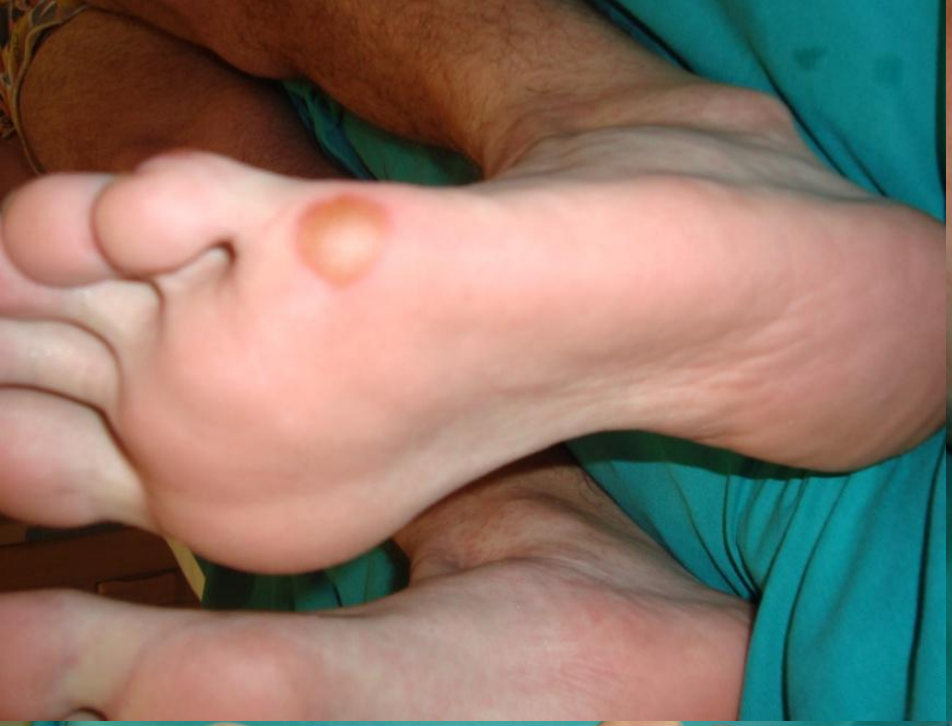
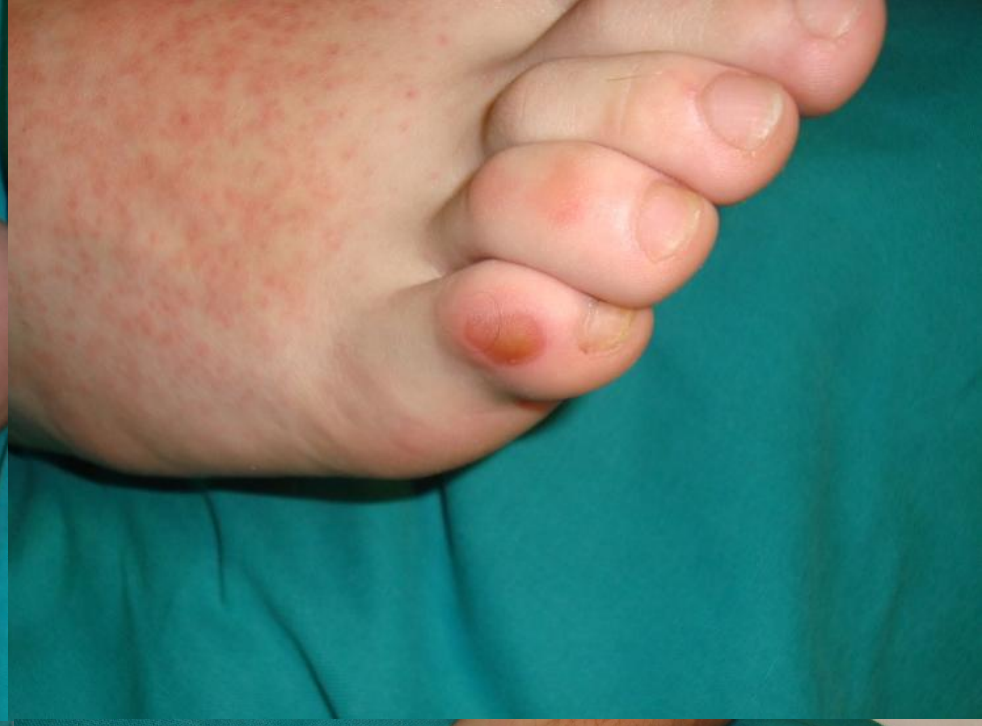
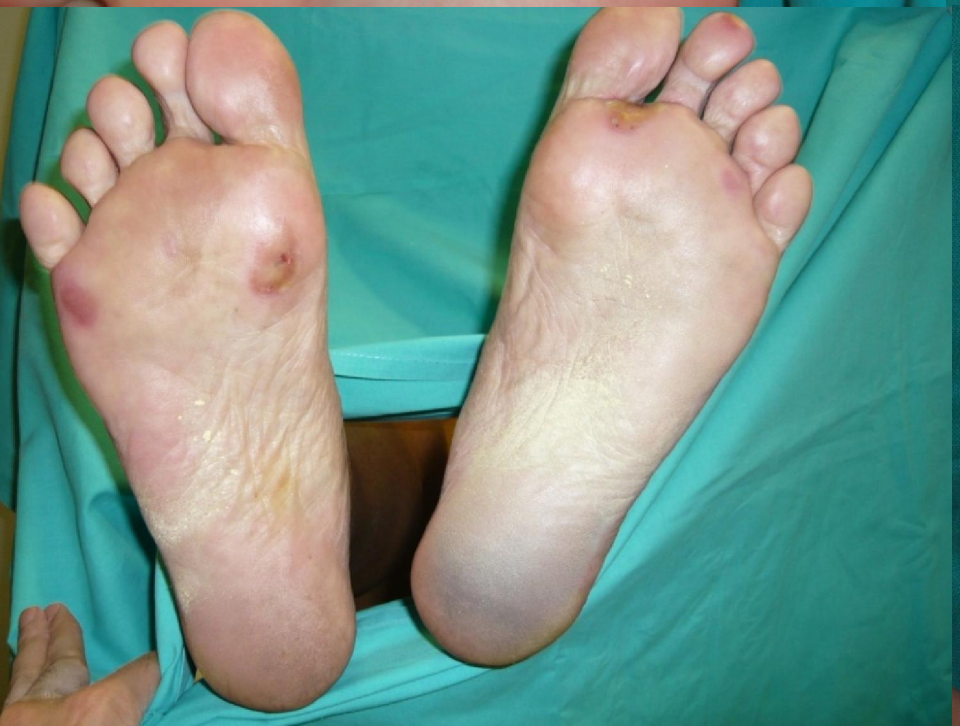
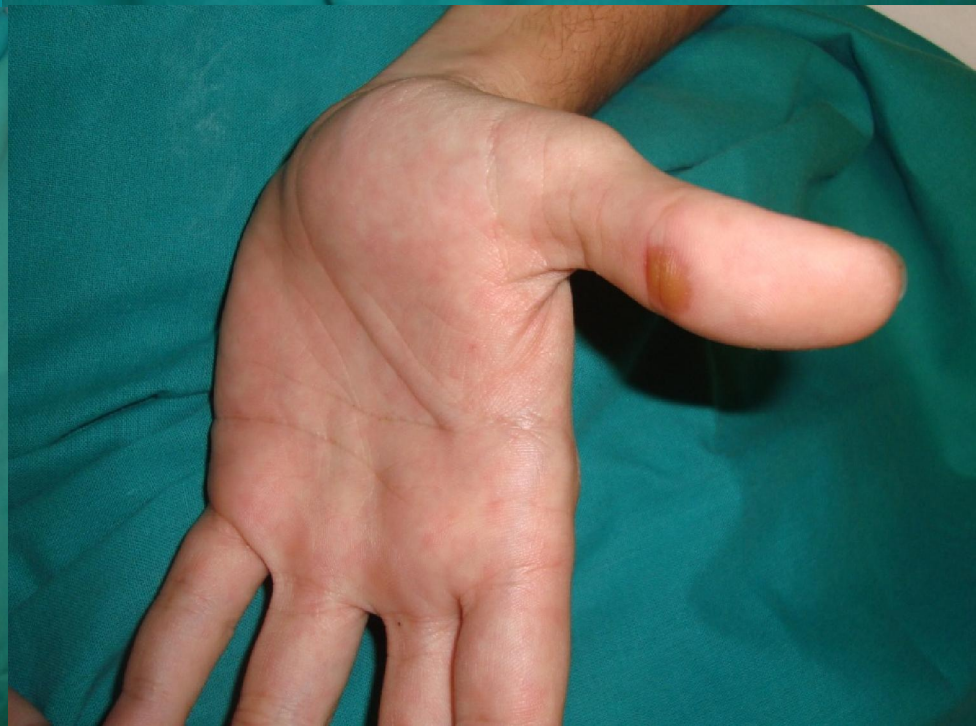
- Muy frecuente
- Sorafenib, sunitinib, vemurafenib, dabrafenib
- Dosis dependiente
- Importantes diferencias con el eritema acral inducido por QT convencional

- Frecuente toxicidad limitante de dosis
- Lesiones hiperqueratosicas focales en palmas y plantas
- Zonas de presión (inducidas por trauma)

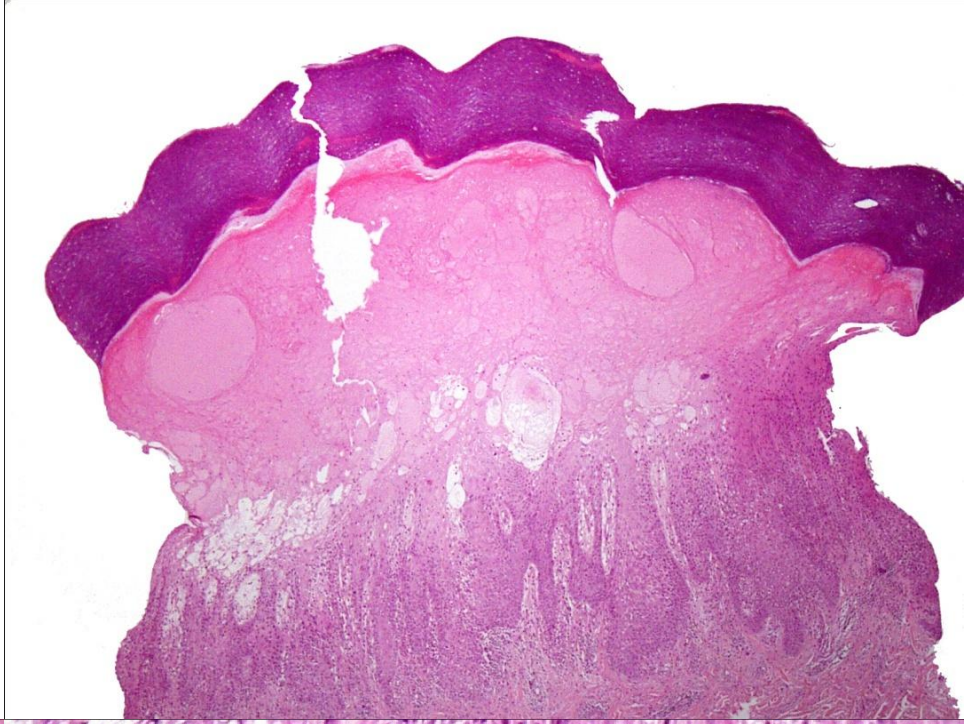


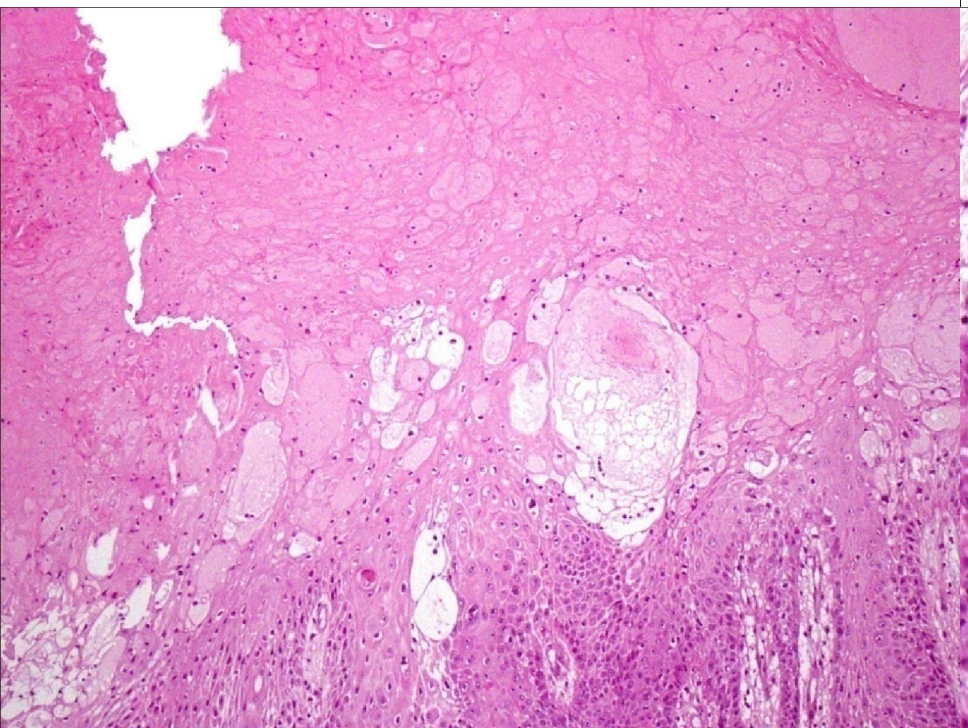


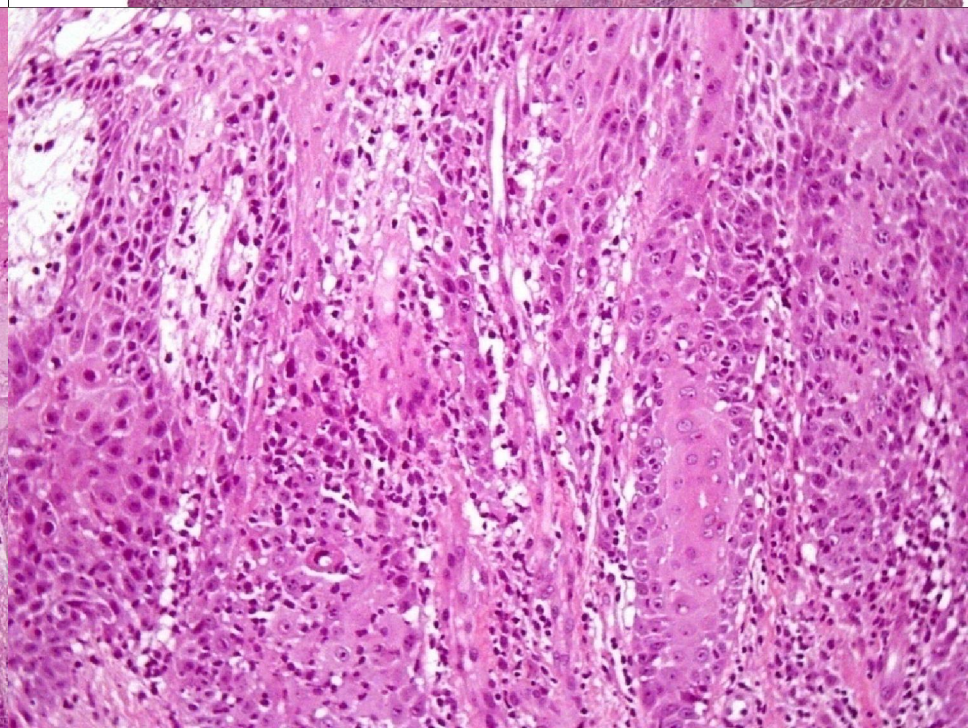


- Hiperqueratosis,papilomatosis y acantosis
- Degeneración hidrópica de la epidermis media, con balonizacion
- Edema intra y extracelular
- Ausencia de queratinocitos necróticos o atipicos







Diferencias entre Eritema acral QT convencional y síndrome pie mano de los ITK

ERITEMA ACRAL DE LA QUIMIOTERAPIA CONVENCIONAL	SINDROME PIE - MANO DE LOS INHIBIDORES MUTIKINASA
Eritema y edema difuso y simétrico	Hiperqueratosis localizada
Daño glándulas ecrinas por excreción sudoral del fármaco	Defecto en la reparación celular por inhibición PDGFr
Histopatología de citotoxicidad inducida por la quimioterapia	Degeneración vacuolar de la epidermis media, con hiperqueratosis y acantosis

Muchas gracias

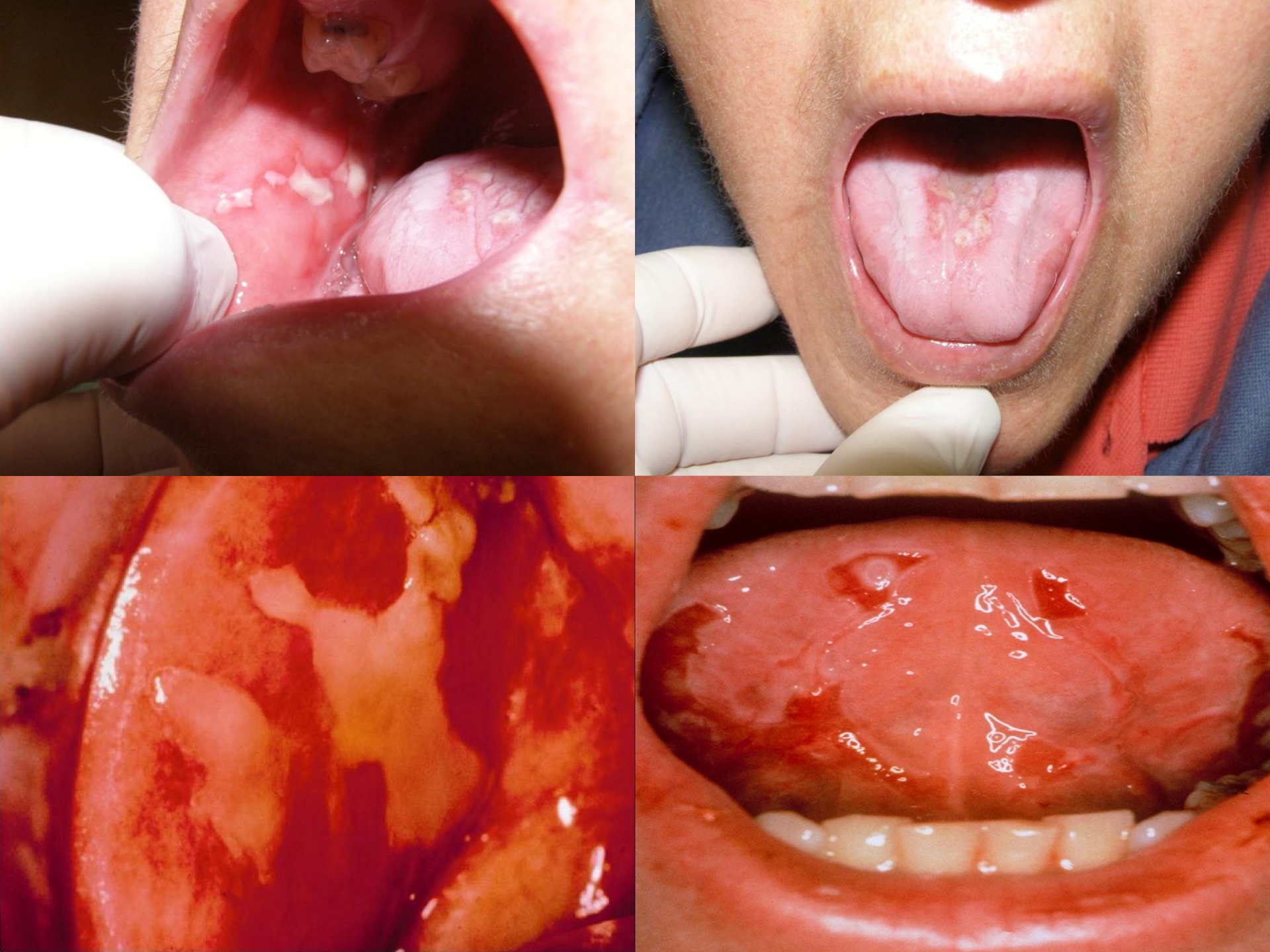
osanmartinj@gmail.com

Inhibidores m-TOR. Ulceras orales

- Sirolimus, everolimus, temsirolimus, deferolimus
- Cáncer de ovario, renal, mieloma y transplantes
- Clasificadas inicialmente como mucositis orales, por similitud con la quimioterapia convencional, siendo publicadas así
- Sin embargo, la historia natural, los efectos adversos asociados y la presentación clínica no son coherentes con ese diagnóstico

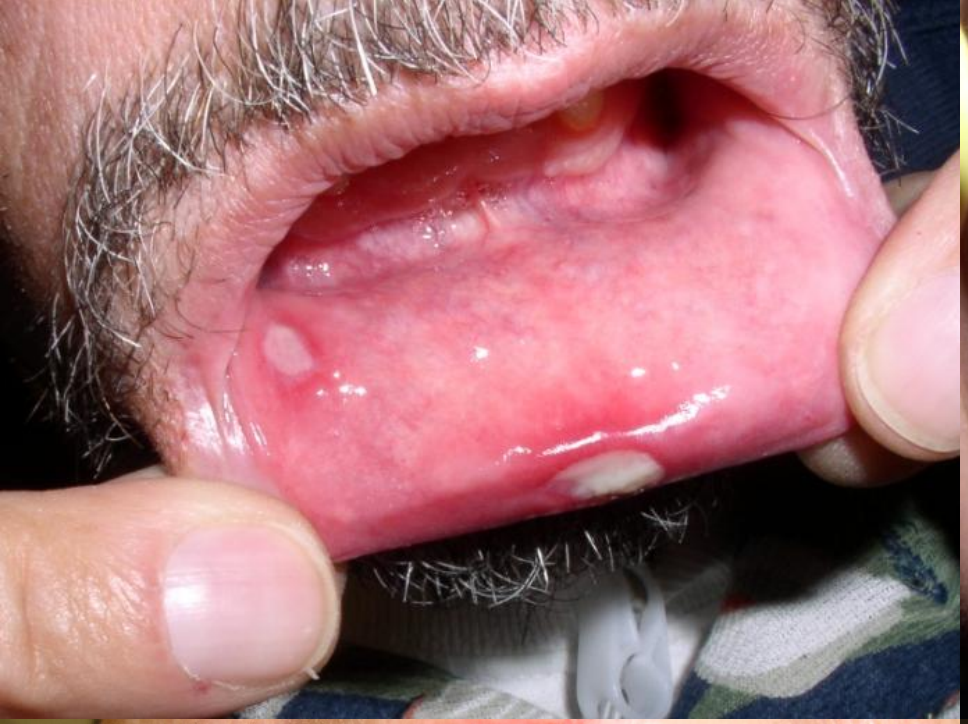
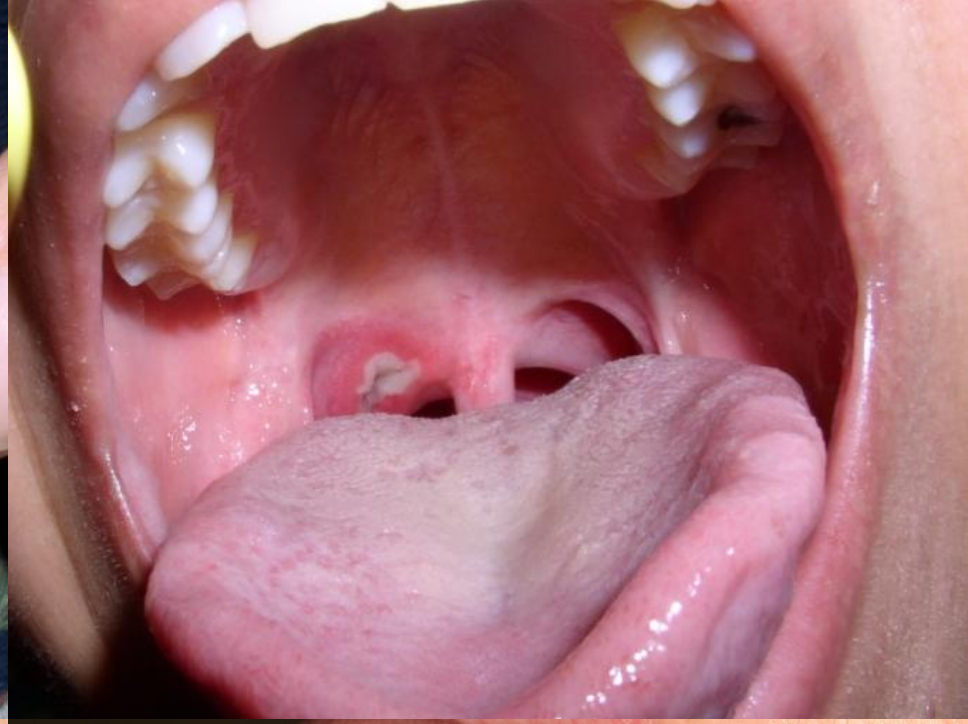
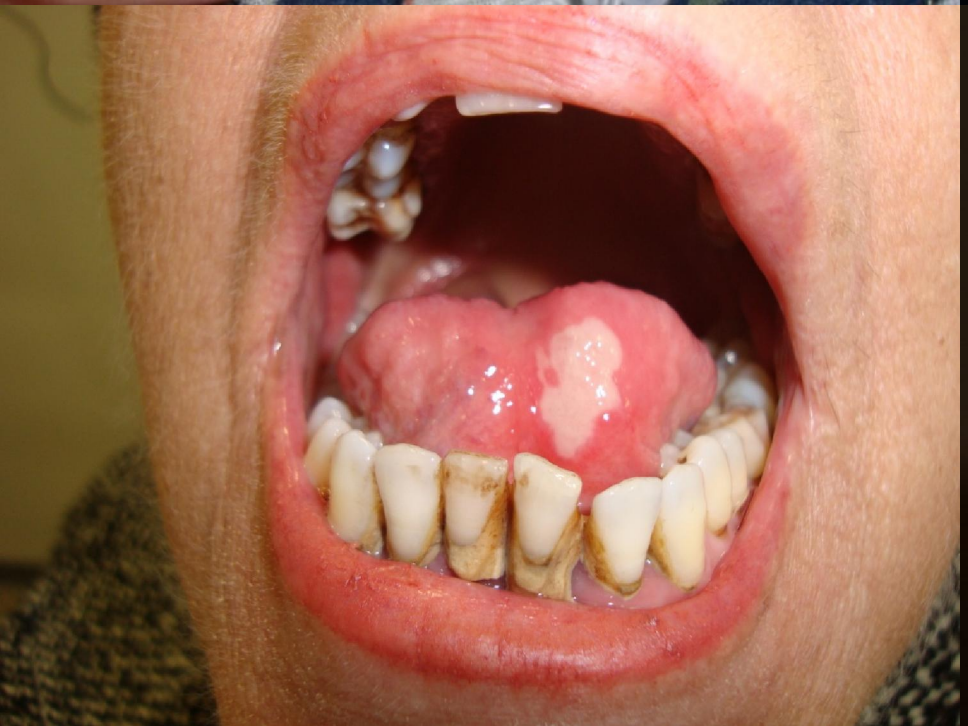
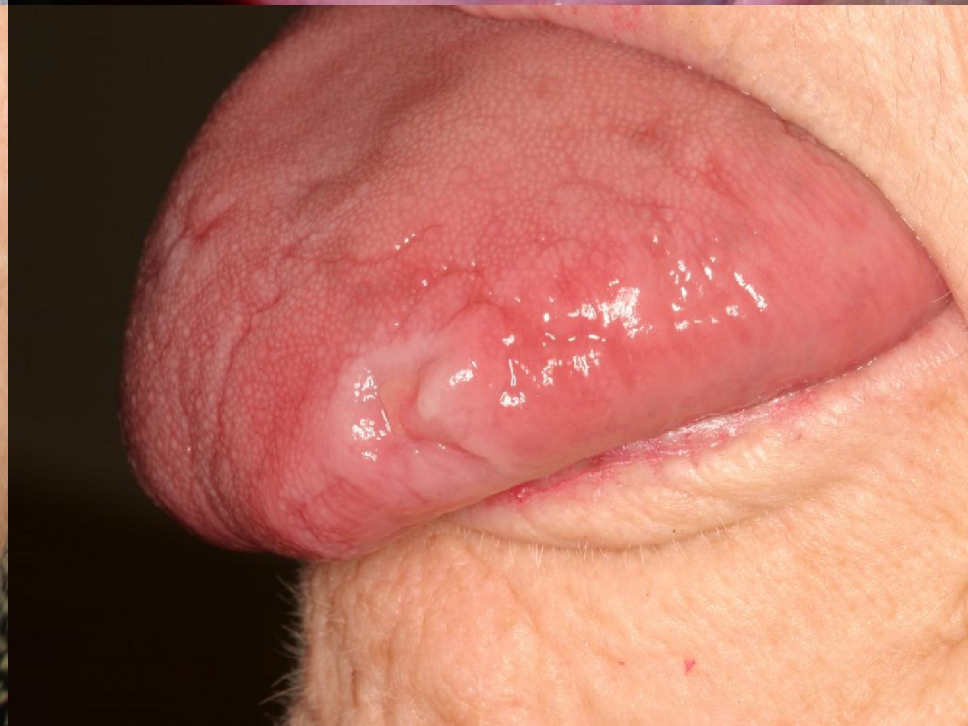
Mucositis oral inducida por citostáticos

- Desarrollo gradual de lesiones ulcerativas Ulcerative phase develops gradually
- Ulceras sin morfologia específica
- Ulceras revestidas por pseudomembrana
- Afectan a mucosa móvil y fija
- Bordes poco definidos y eritematosos
- Generalmente asociadas a otras toxicidades de la QT (gastrointestinal)



La apariencia clínica de las úlceras orales inducidas por inhibidores de mTOR es de aftosis

- Lesiones ulcerosas, delimitadas, ovales y de tamaño pequeño-mediano
- Las lesiones no son tan profundas como en la mucositis por qt convencional
- Centro con revestimiento fibrinoso amarillento
- Lesiones localizadas en la zona de la mucosa móvil (labios, mejillas, suelo de boca, paladar blando y lengua)

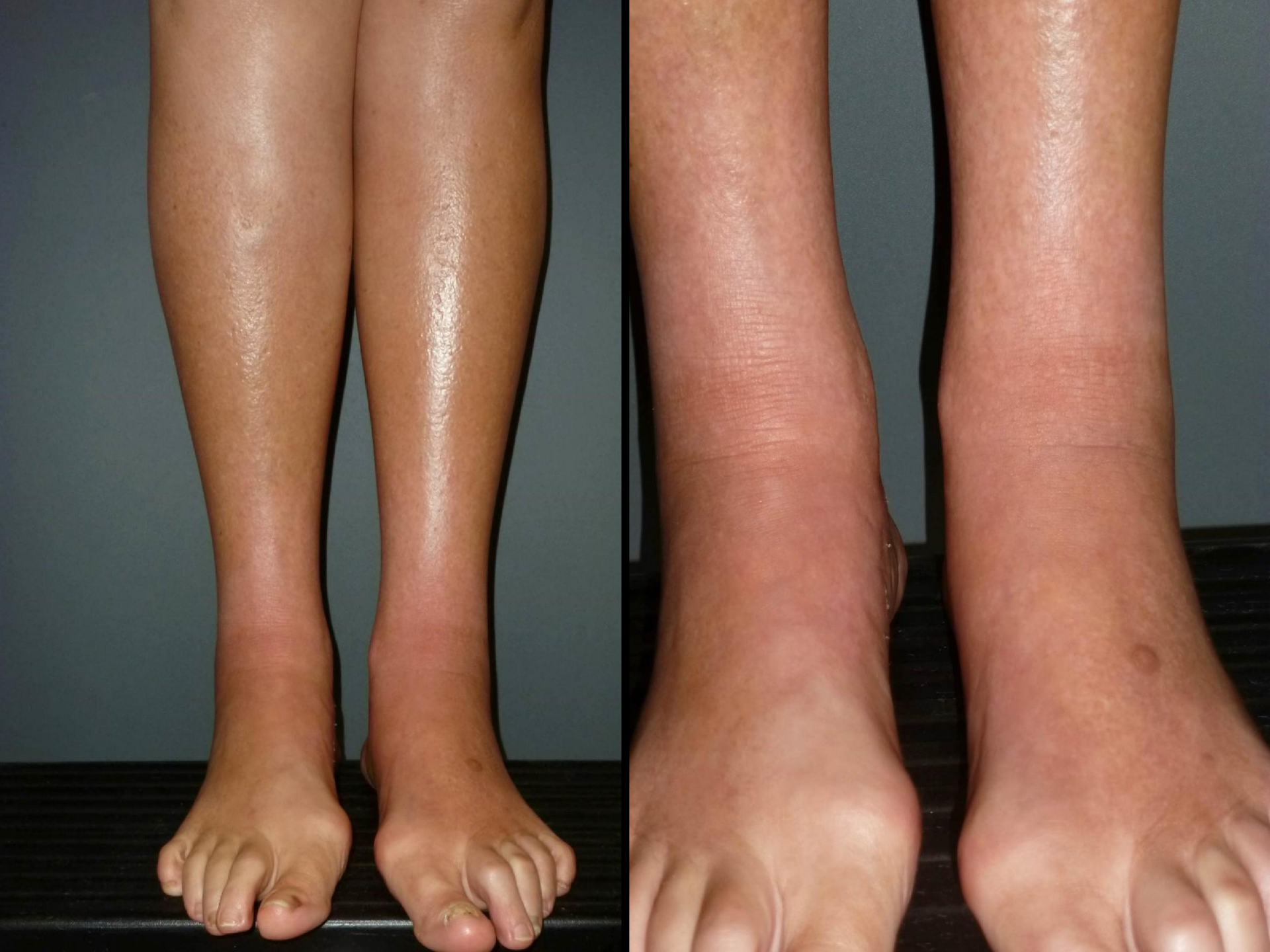





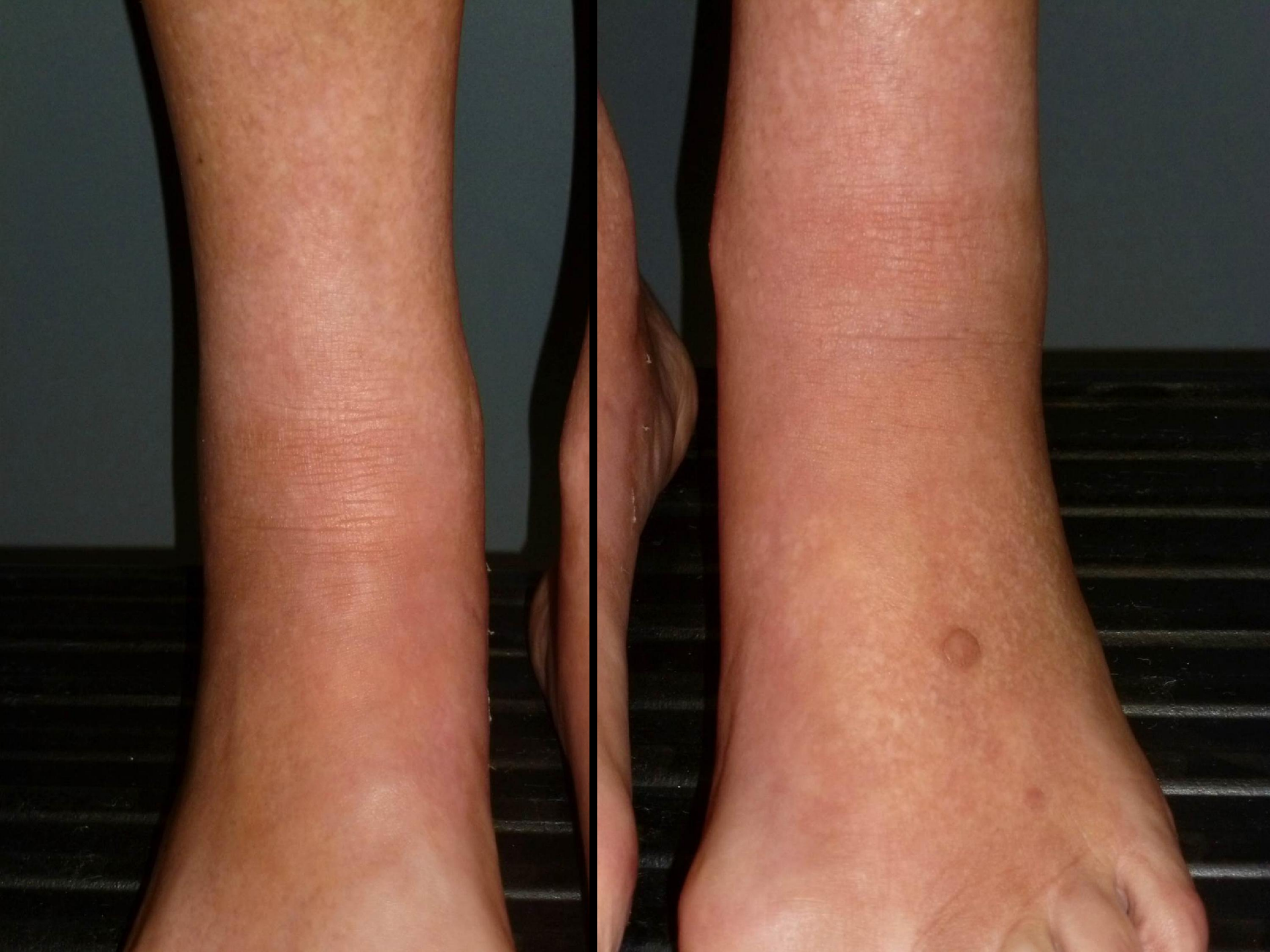
Curso clínico de las aftosis inducidas por mTOR Inh

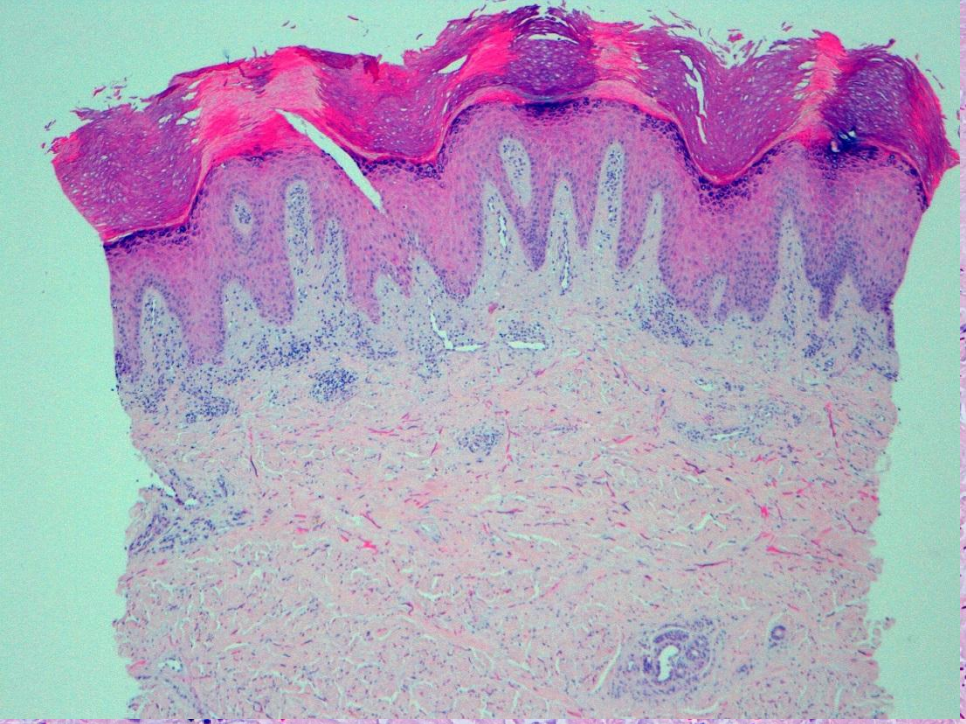
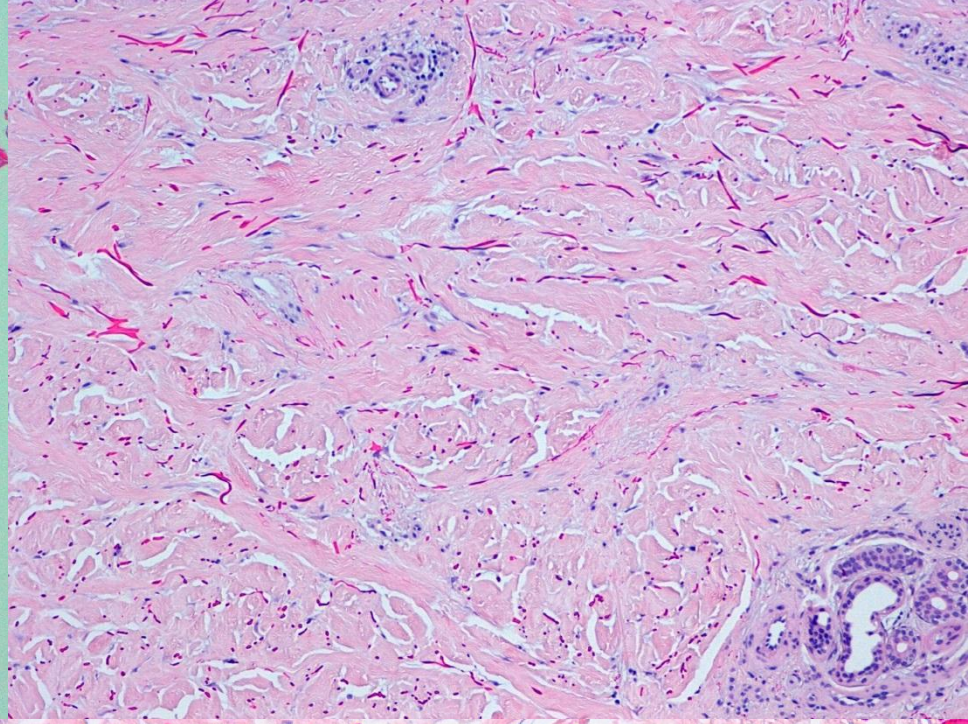
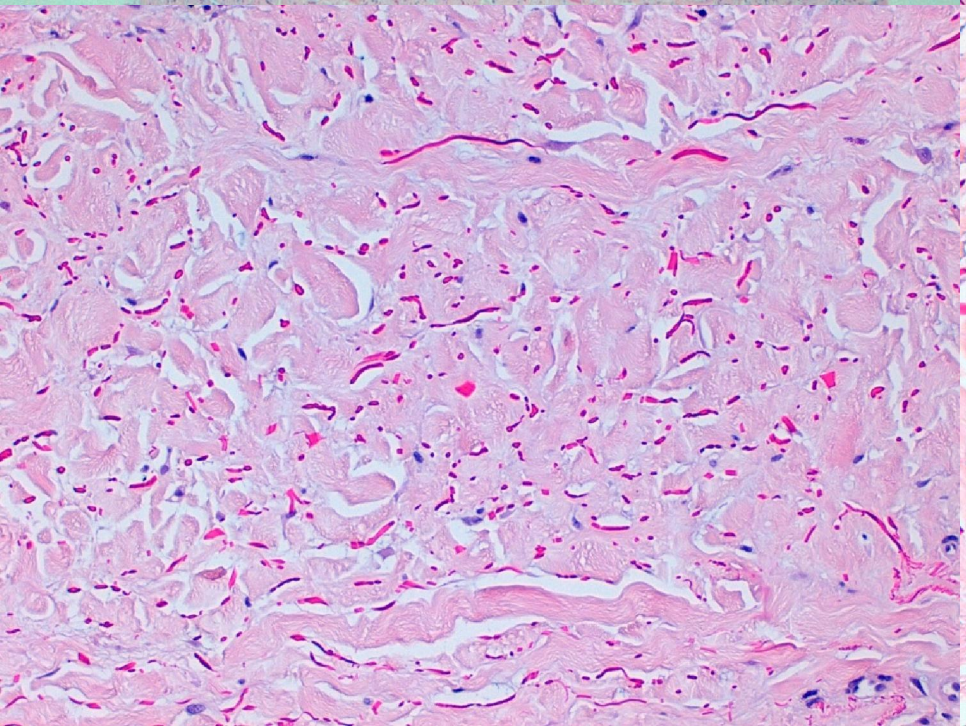
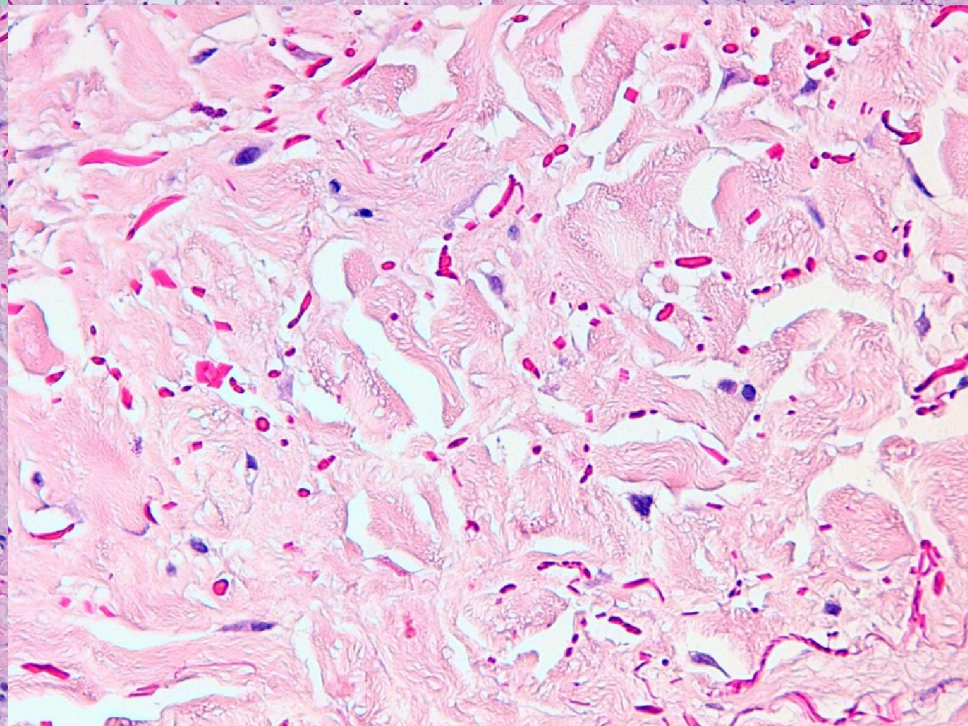
- Inicio precoz (5º día de tto)
- Dolorosas con la movilidad
- Tendencia a la resolución espontánea
- Buena respuesta a esteroides tópicos

Esclerodermia inducida por taxanos

- No es un efecto secundario infrecuente
- Afectación exclusivamente cutánea, sin repercusión sistémica
- **Relacionada con la dosis total acumulada de TAXANOS**
- Primer fenómeno: EDEMA, que despues es seguido por INDURACIÓN CUTÁNEA
- Edema de piernas frecuente durante el tratamiento con taxanos
- Tratamiento: prednisona oral y ajuste de dosis de taxano



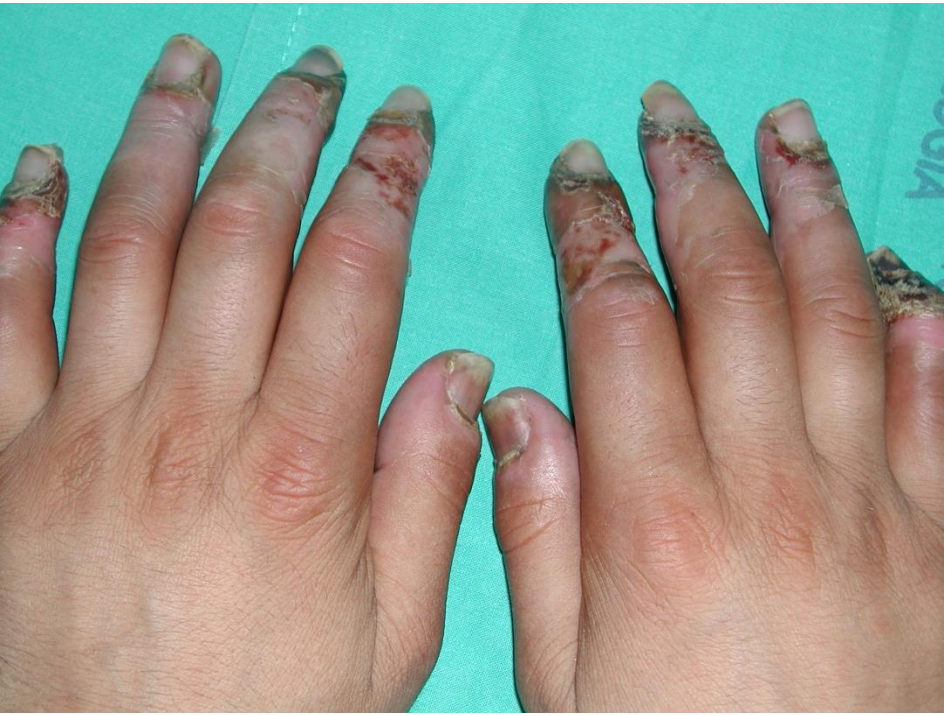


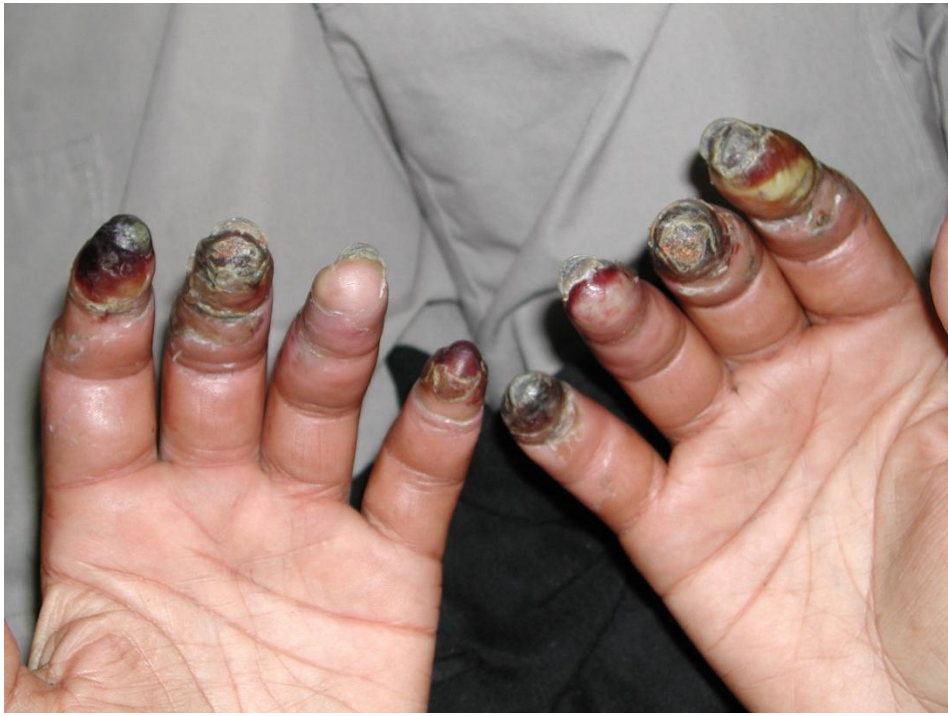





Patient	Age (years)/sex	Primary tumour	Regimen (mg m^{-2})	Onset of oedema/skin sclerosis[a] (months)	Total cumulative dose[b] (mg m^{-2})	Location of sclerosis	Total skin thickness score	Therapy	Outcome
1	37/F	Left breast	T (60–75) P (80)	5/17	T (1380) P (960)	All extremities	18	Drug change Steroid systemic therapy	Slight improvement
2	53/F	Right breast	T (60)	5/10	T (720)	Lower extremities	8	Steroid ointment Rehabilitation	No change
3	66/F	Left breast	T (60)	6/16	T (1200)	Left upper and lower extremities	14	Drug discontinuance Steroid ointment Rehabilitation	Slight improvement
4	46/F	Right breast	T (60–75)	6/11	T (1125)	Lower extremities	12	Drug change Steroid systemic therapy Rehabilitation	Slight improvement
5	61/F	Left breast	T (60–75) P (80)	12/17	T (1080) P (1120)	Lower extremities	Unknown	Drug change Steroid ointment	Unknown

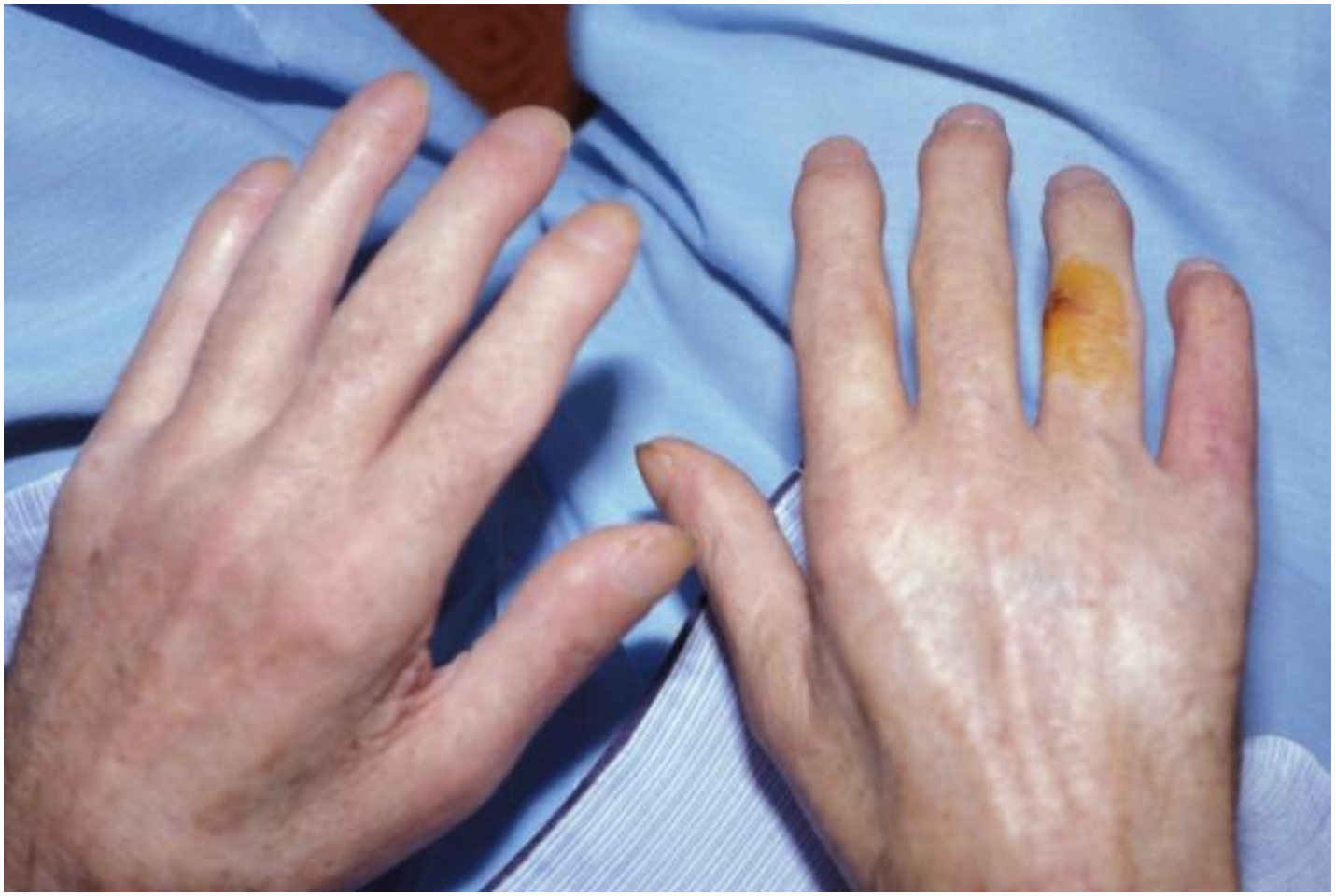
T, docetaxel; P, paclitaxel. [a]Onset of oedema/skin sclerosis = the period from the initiation of taxane therapy to the onset of oedema/skin sclerosis. [b]Total cumulative dose = the cumulative dose of taxanes at the time of onset of skin sclerosis.

Síndrome de Raynaud (Bleomicina)





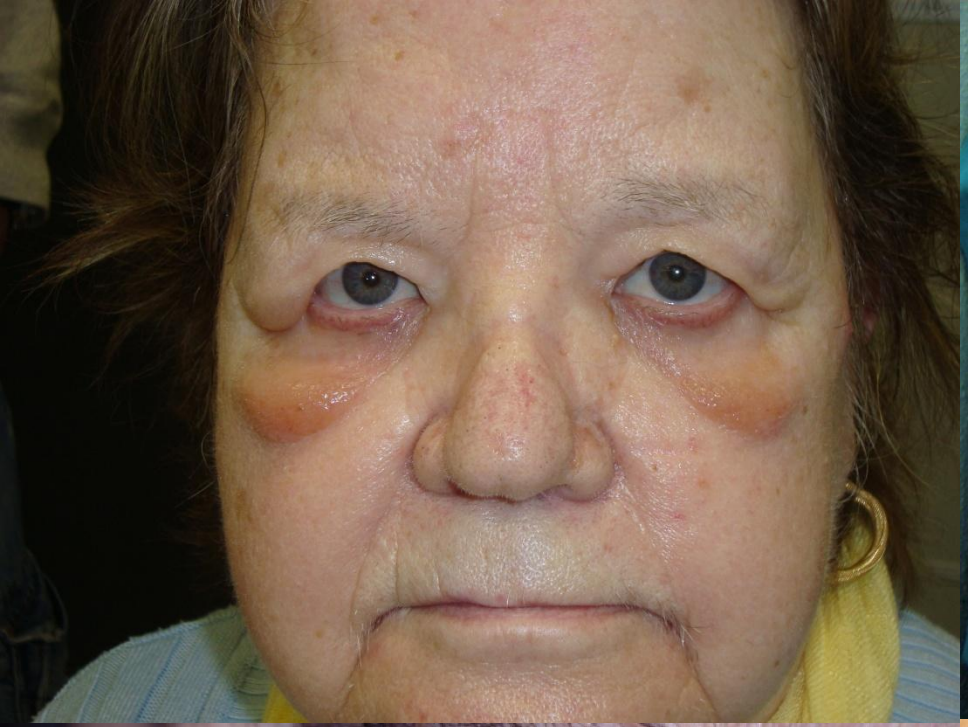
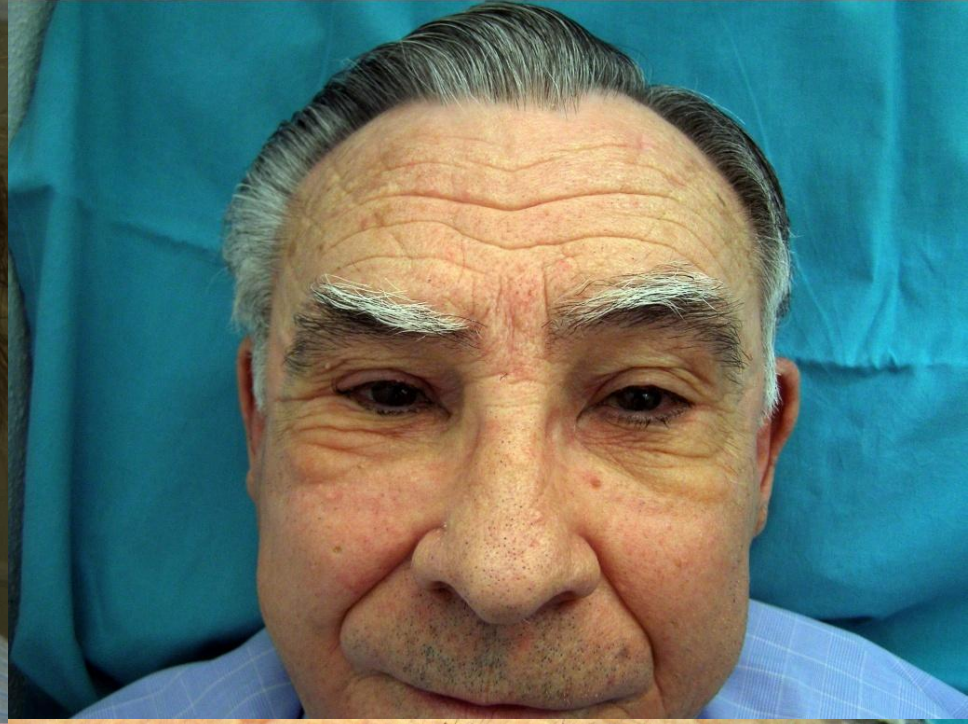
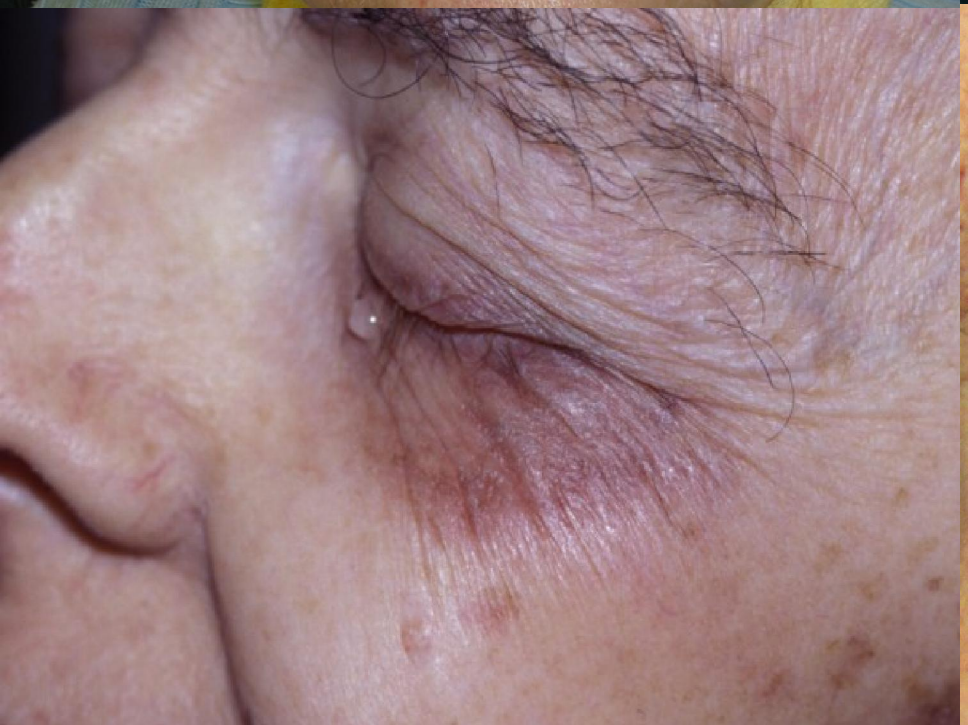
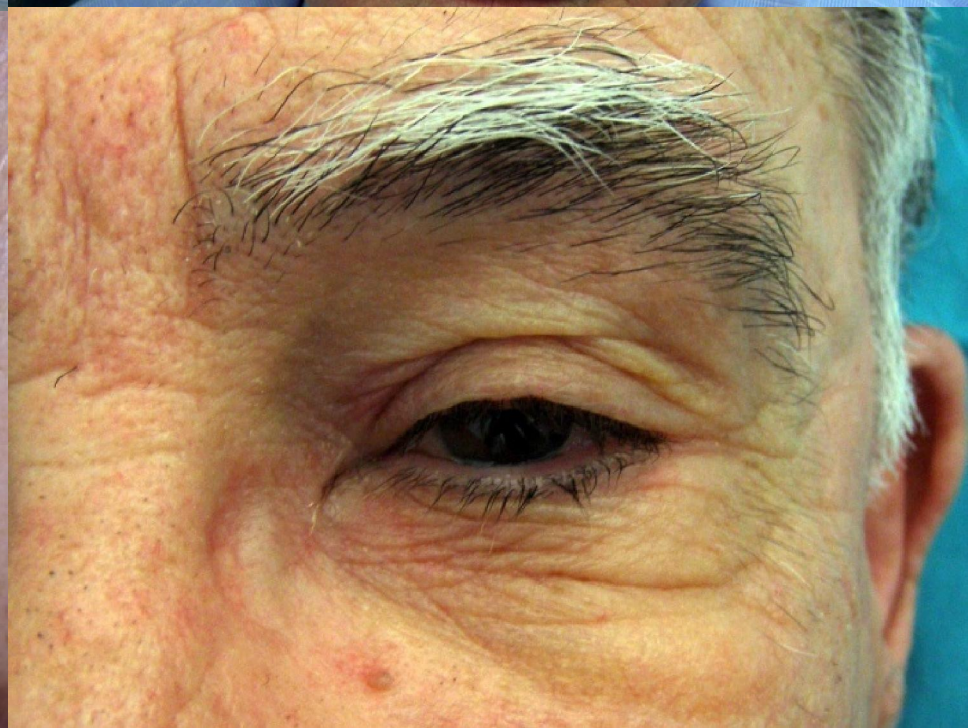
Esclerodactilia (Bleomicina y Taxanos)

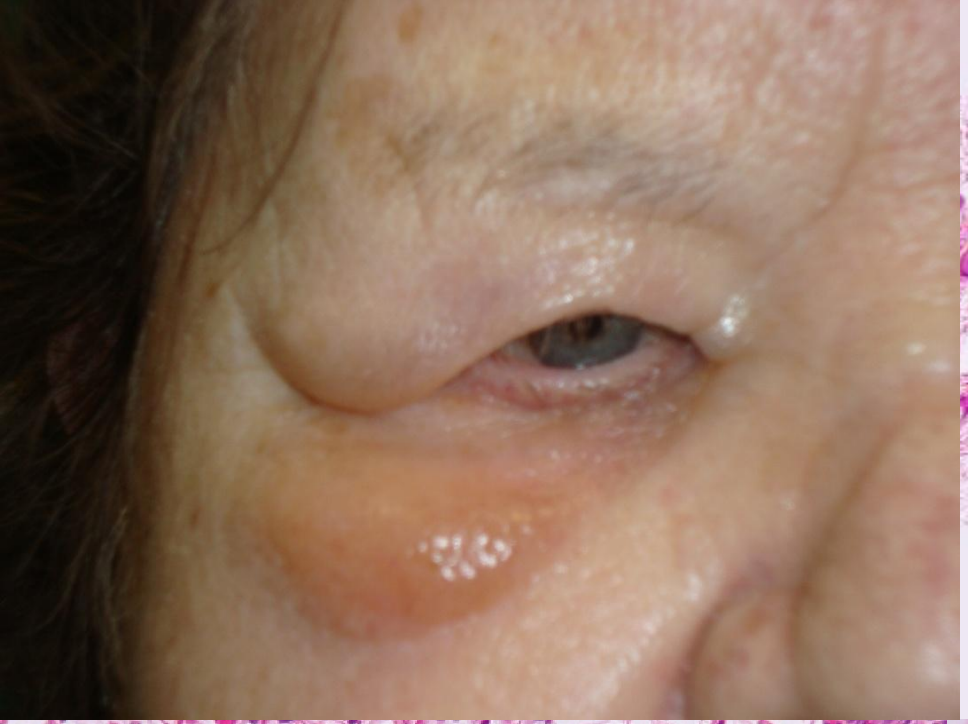
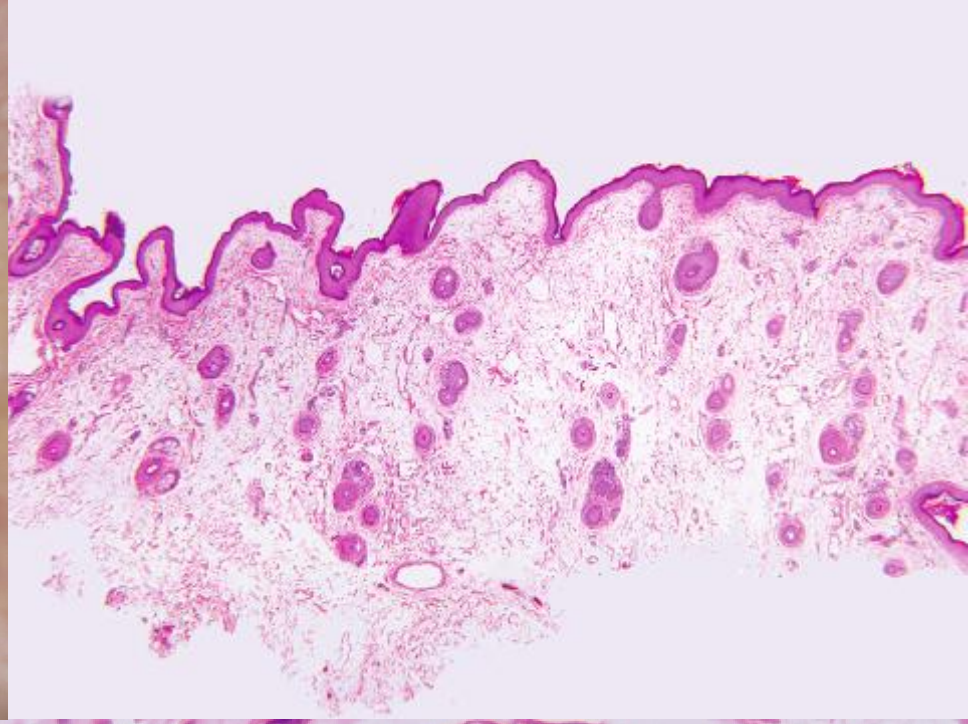
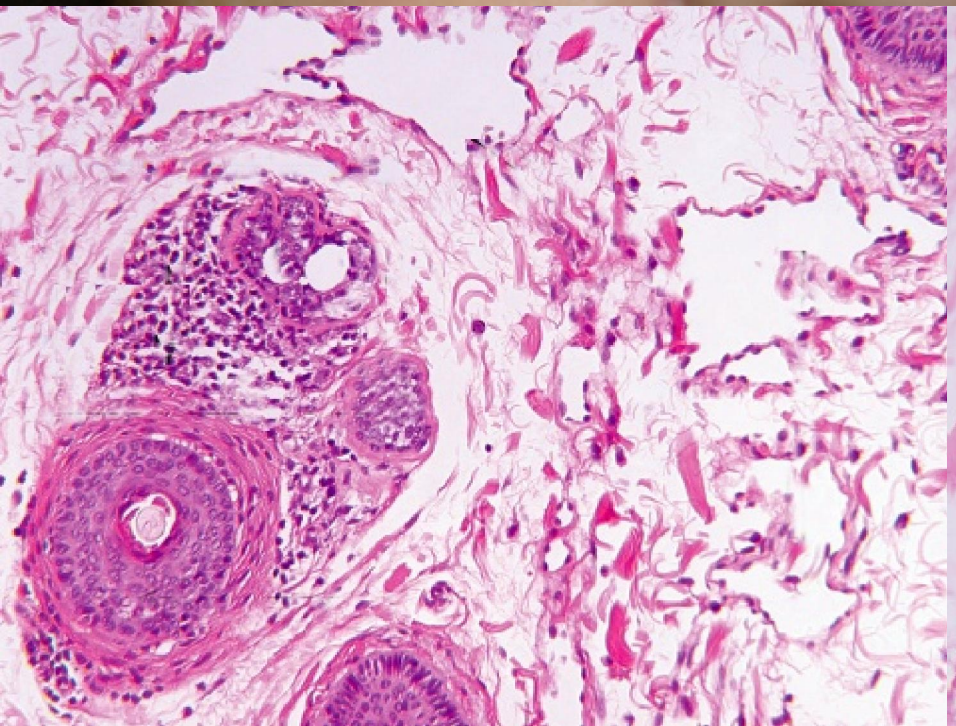
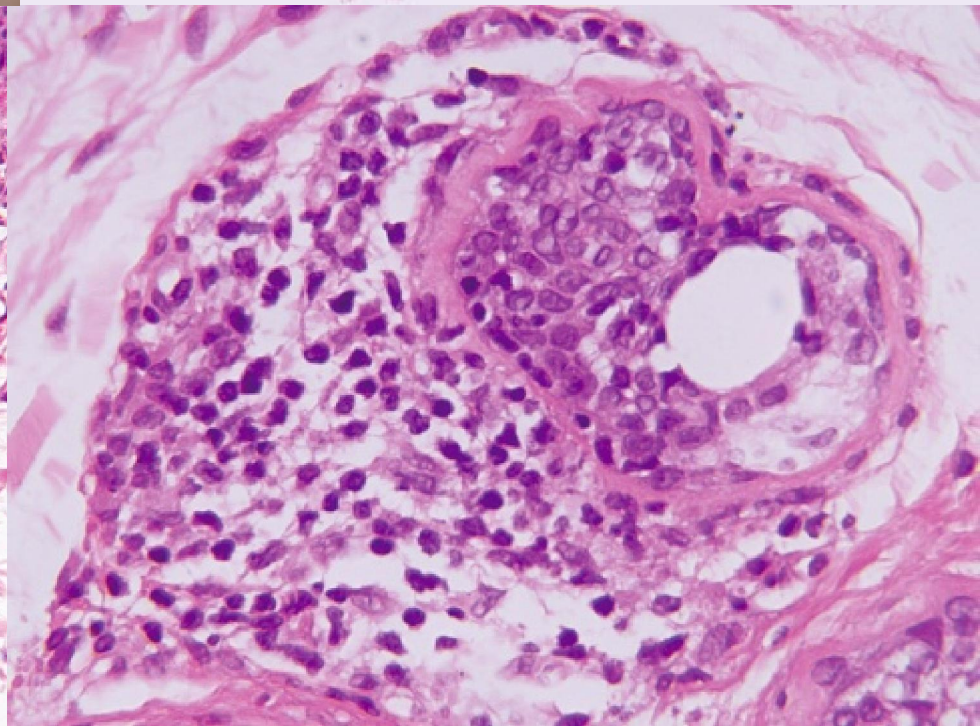


MULTIKINASE INHIBITORS EDEMA

- Imatinib, less frequent Sunitinib and Sorafenib
- Dose-dependent
- Most common: Periorbital, esp after 2 months (1-400 days)
- Appears in up to 70% patients with imatinib
- 20% with concomitant peripheral edema

J Ocul Pharmacol Ther 2003; 19(4): 371

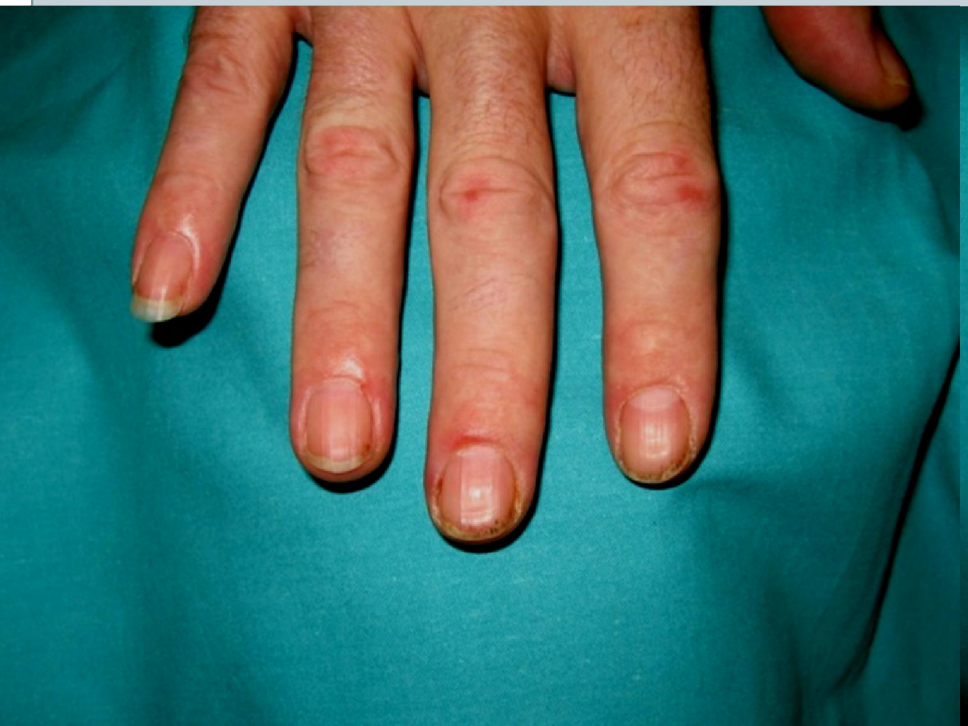





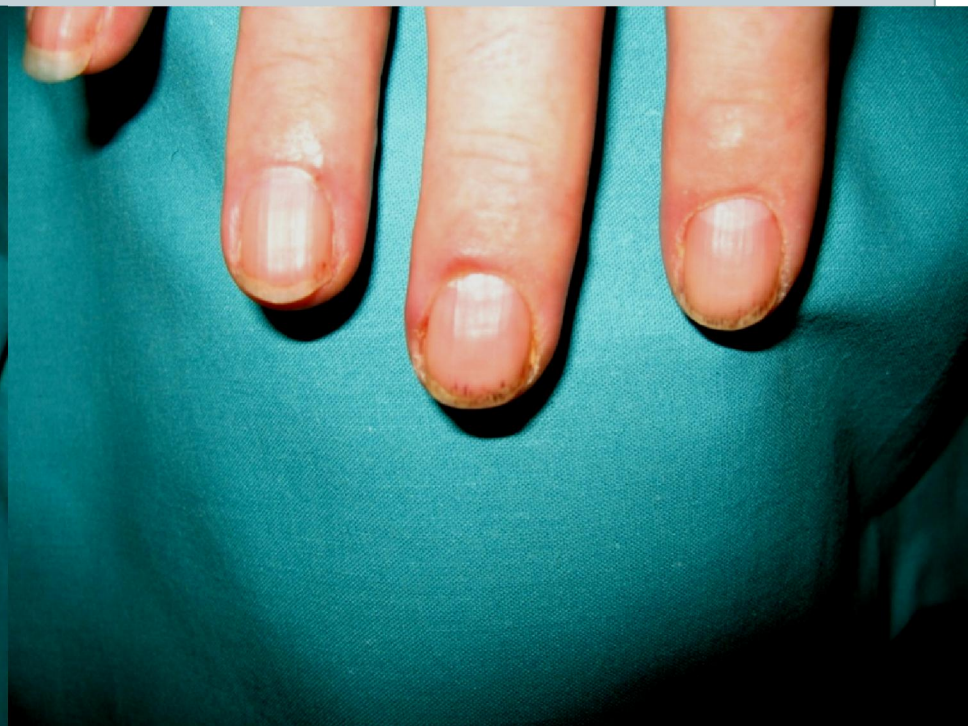
MULTIKINASE INHIBITORS EDEMA

- **Pathogenesis**
- Inhibition of platelet-derived growth factor receptor (PDGFR) signaling by the drug.
- PDGFR signaling has been shown to increase the interstitial fluid pressure in the dermis of rodents
- Inhibition of the PDGFR signaling cascade may result in increased capillary permeability and extravasation of fluid
- PDGFR is highly expressed in dermal dendrocytes of periocular area

SPLINTER HEMORRHAGES

- Seen frequently with sunitinib and sorafenib
- Most common skin toxicity
- Blockade of VEGFr (>>> PDGFr) might impair the physiological repair of nail bed capillaries





PSEUDOPORPHYRIA

J Am Acad Dermatol
Volume 63, Number 1

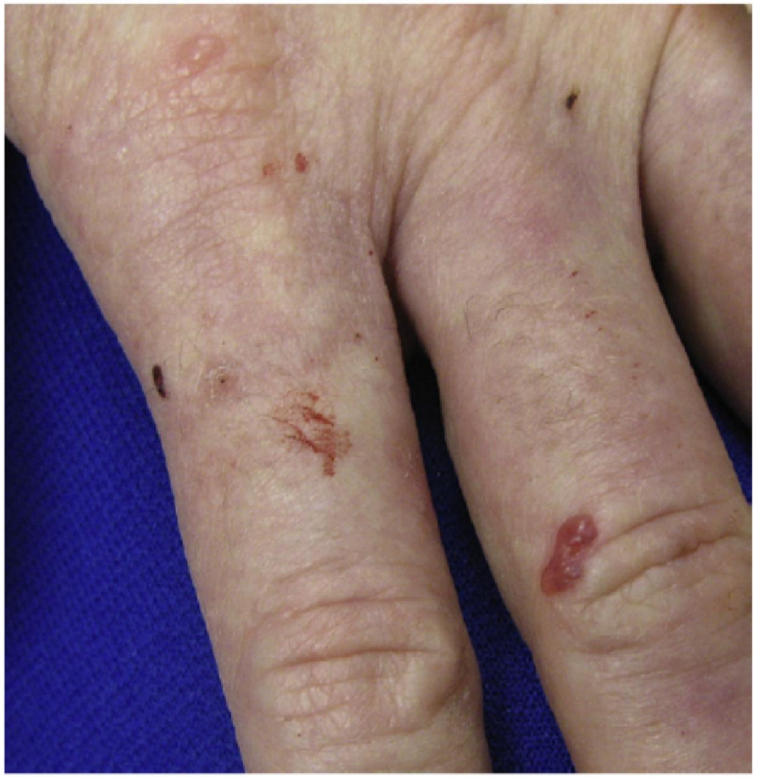


Fig 1. Skin fragility with vesicles on the dorsal surface of the hands that were induced by imatinib.

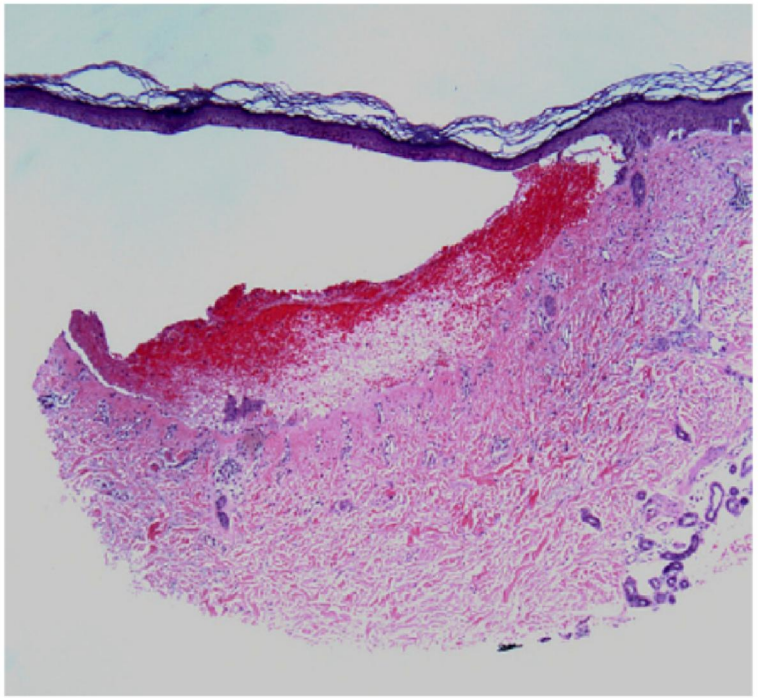
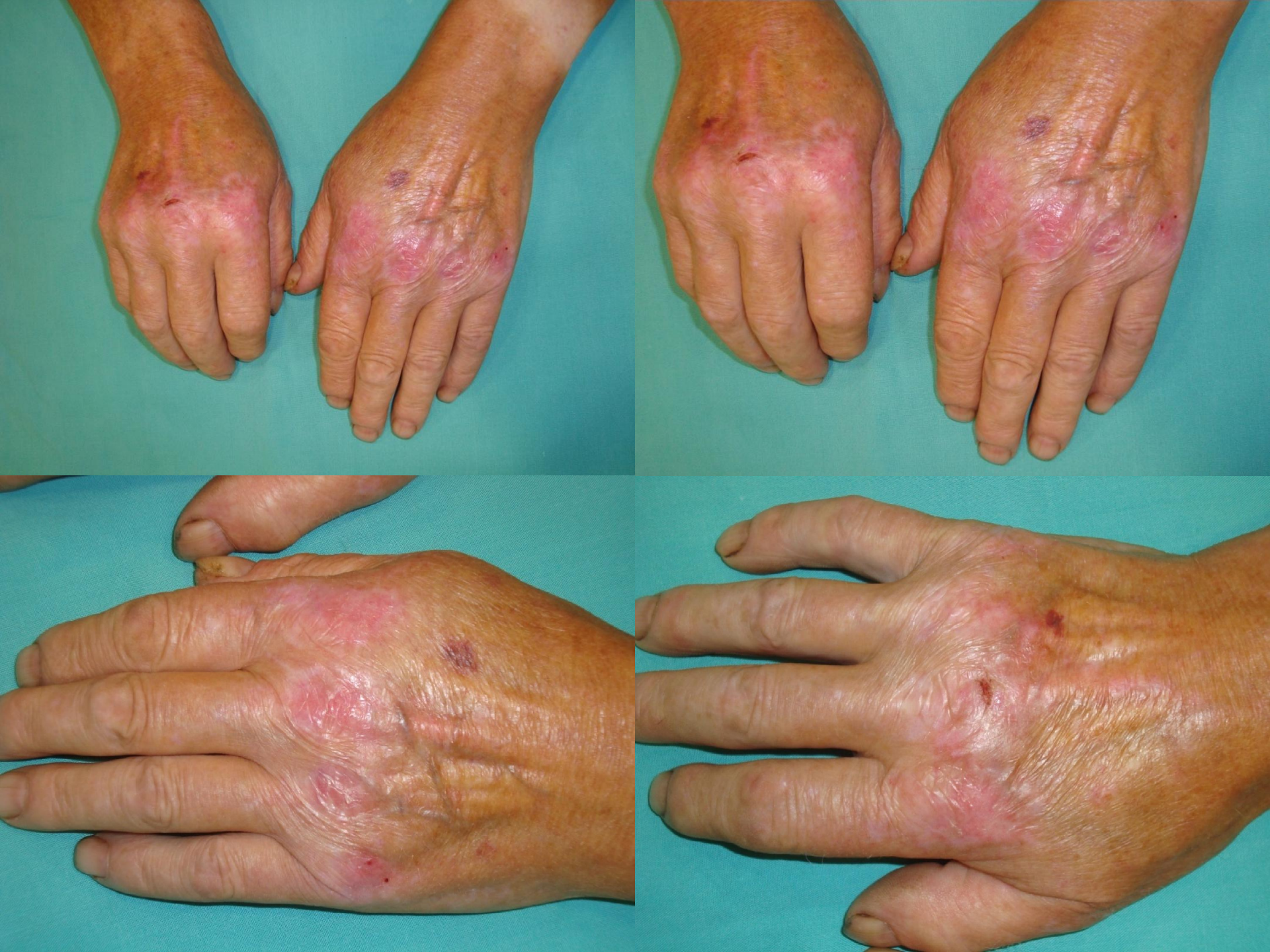
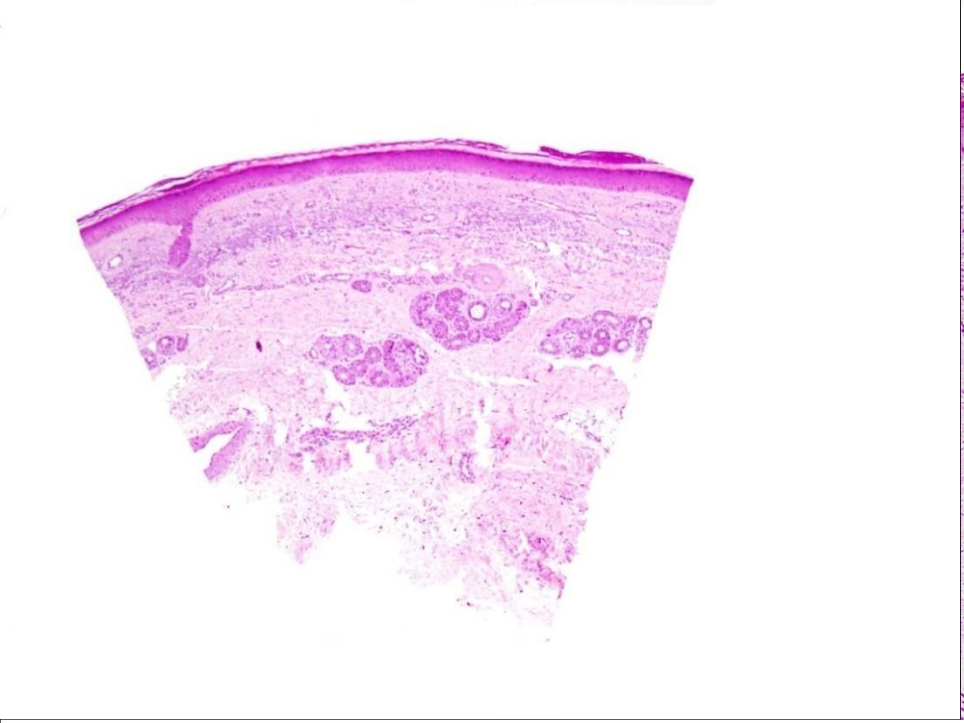
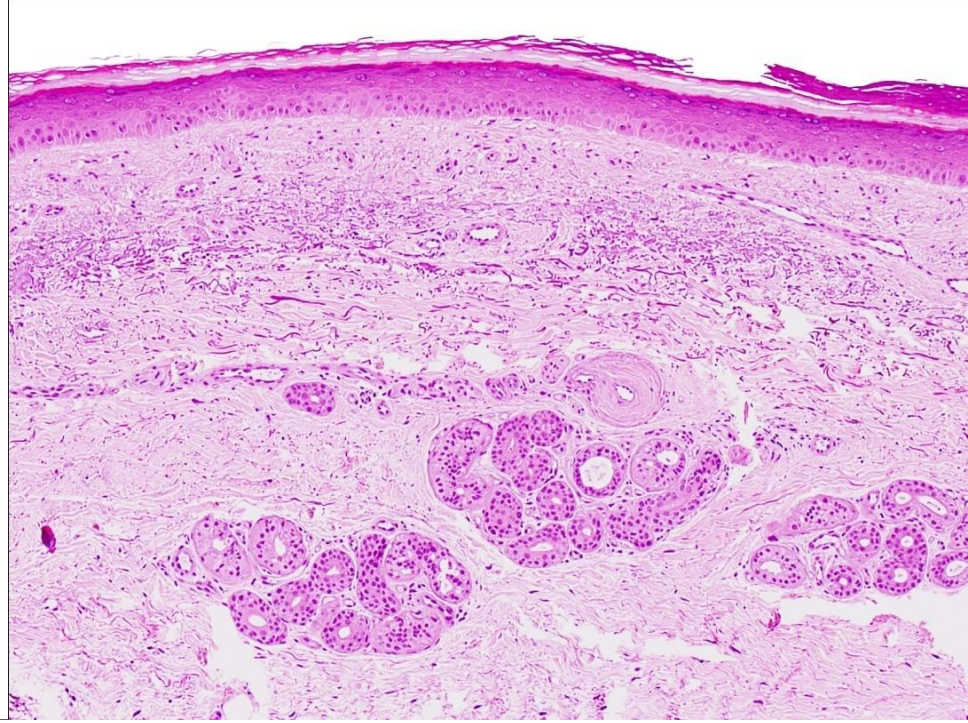
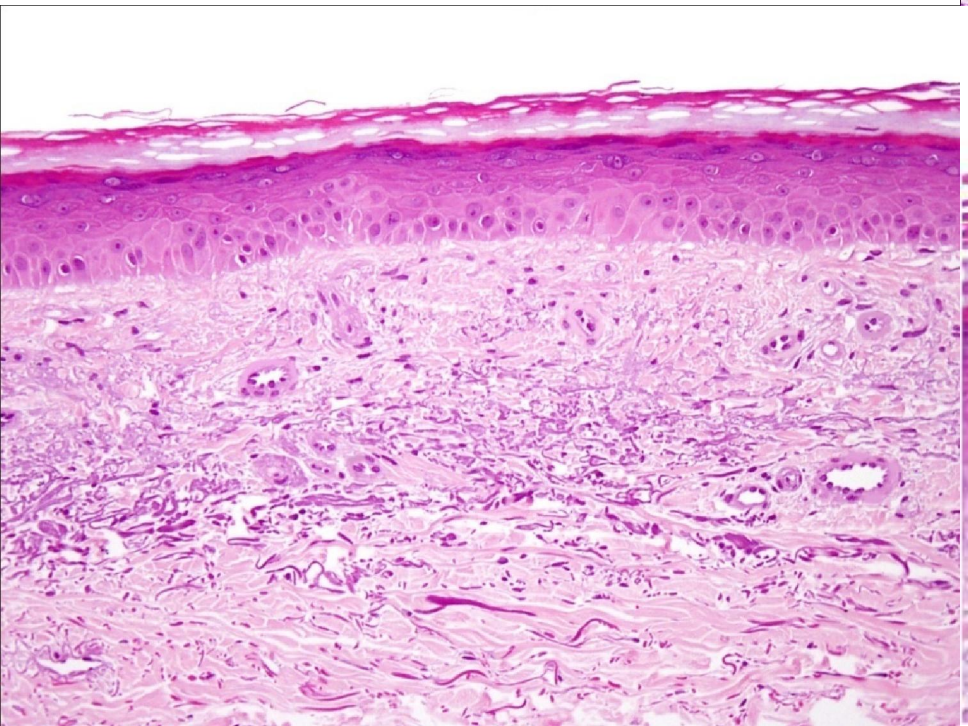
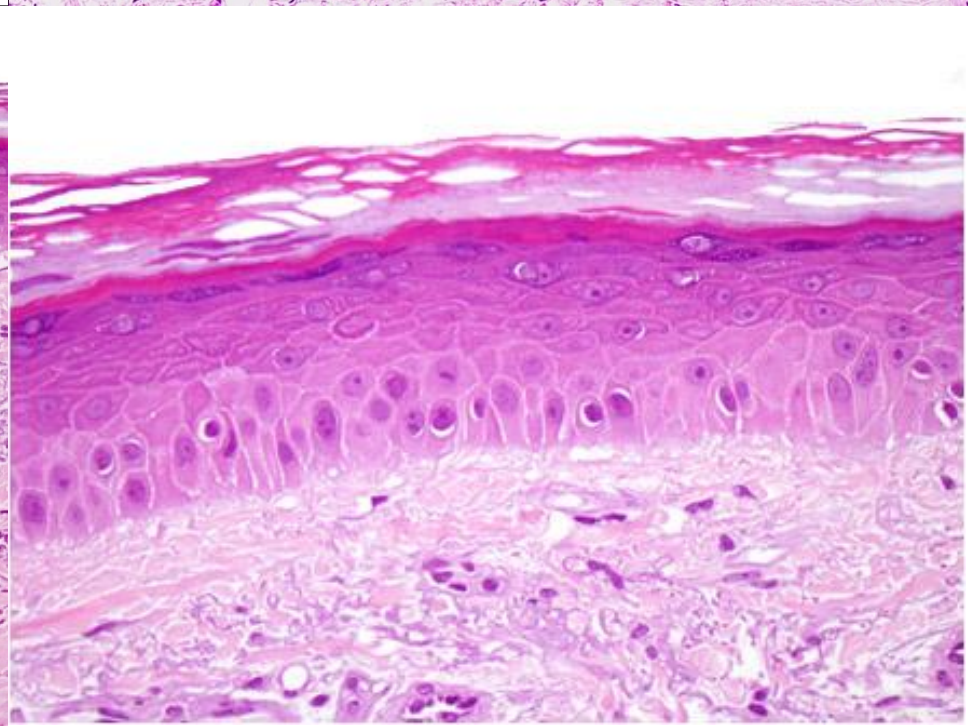


Fig 2. Cell poor, hemorrhagic subepidermal split with thickening of the dermal vasculature. (Courtesy of the University of Pittsburgh Department of Dermatopathology. Hematoxylin–eosin stain; original magnification: ×10.)



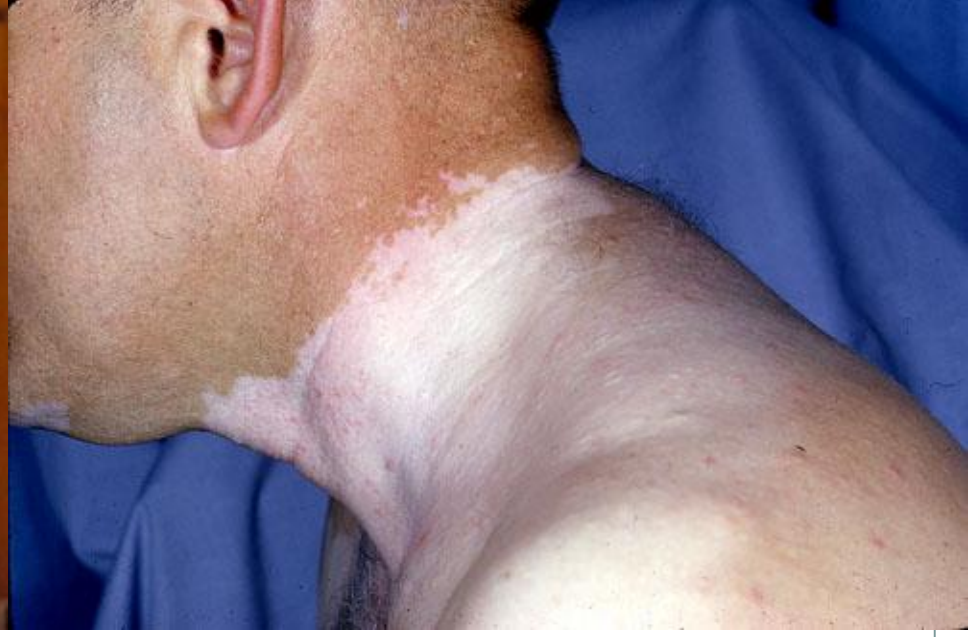
PSEUDOPORPHYRIA

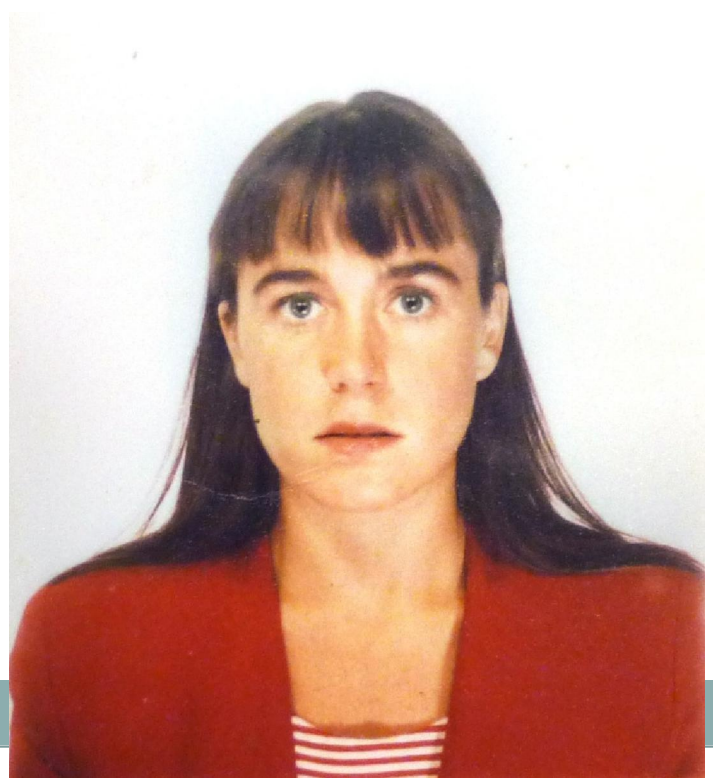
- Pseudoporphyria describes a bullous photosensitivity that clinically and histologically mimics porphyria cutanea tarda.
- No demonstrable porphyrin abnormalities are present
- photosensitizing drug might behave in a similar fashion to porphyrins and target similar structures in the skin
- Atrophy of the skin may make it more susceptible to bruising or tearing.
- Imatinib and Sunitinib are likely to cause this due to the blocking of molecules in skin that are important for its repair and regeneration, both of which occur on a daily basis

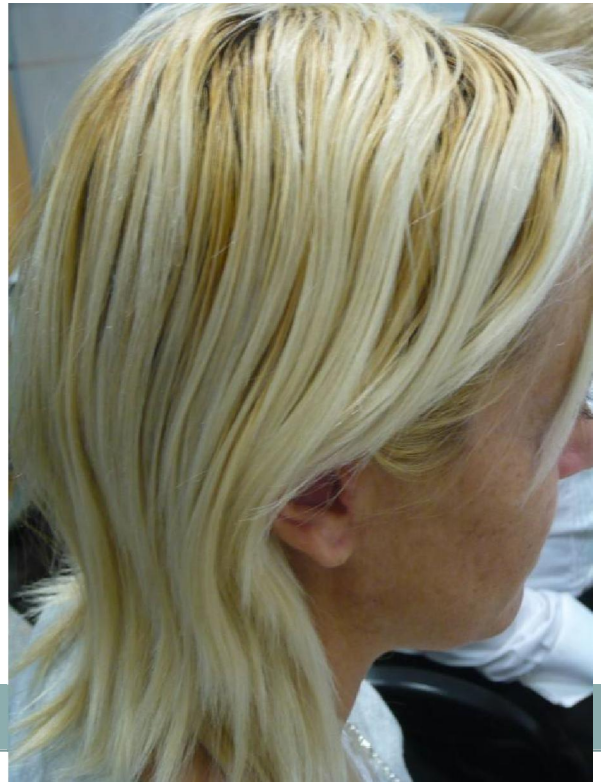
CUTANEOUS HYPOPIGMENTATION INDUCED BY c-kit INHIBITION

- c-kit and its ligand stem cell factor are implicated in melanogenesis, melanocyte homeostasis and UV-B induced pigmentation
- C-kit inhibition may induce depigmentation, hypopigmentation , inhability to tan and hair decoloration
- **Induced by** imatinib, sunitinib y sorafenib

Leong KW et al. Imatinib causes hypopigmentation in the skin. Cancer 2004; 100: 2486



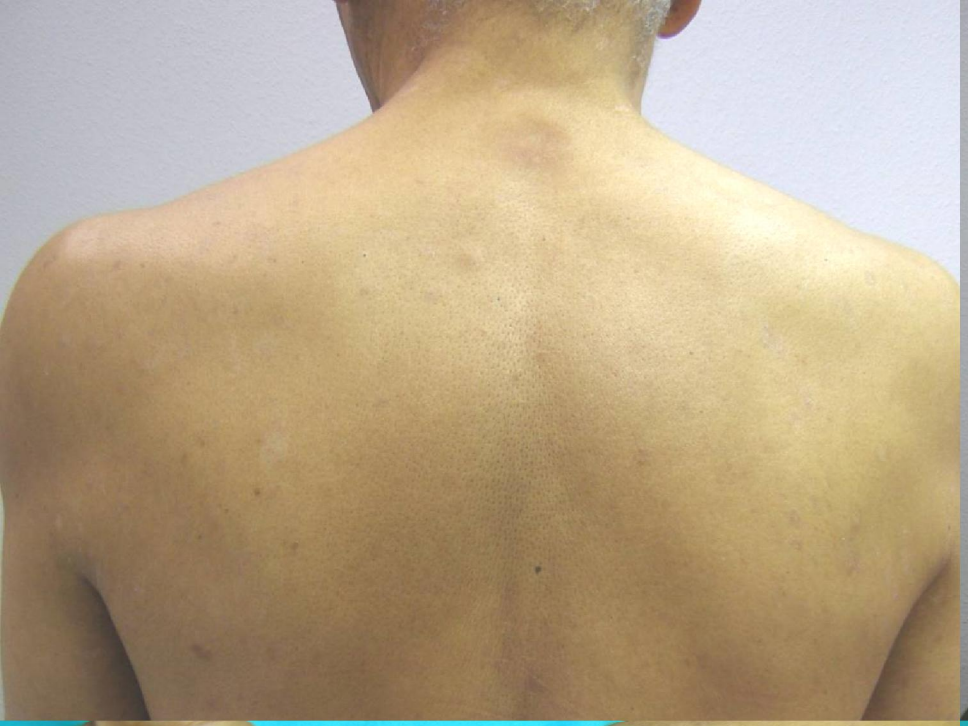
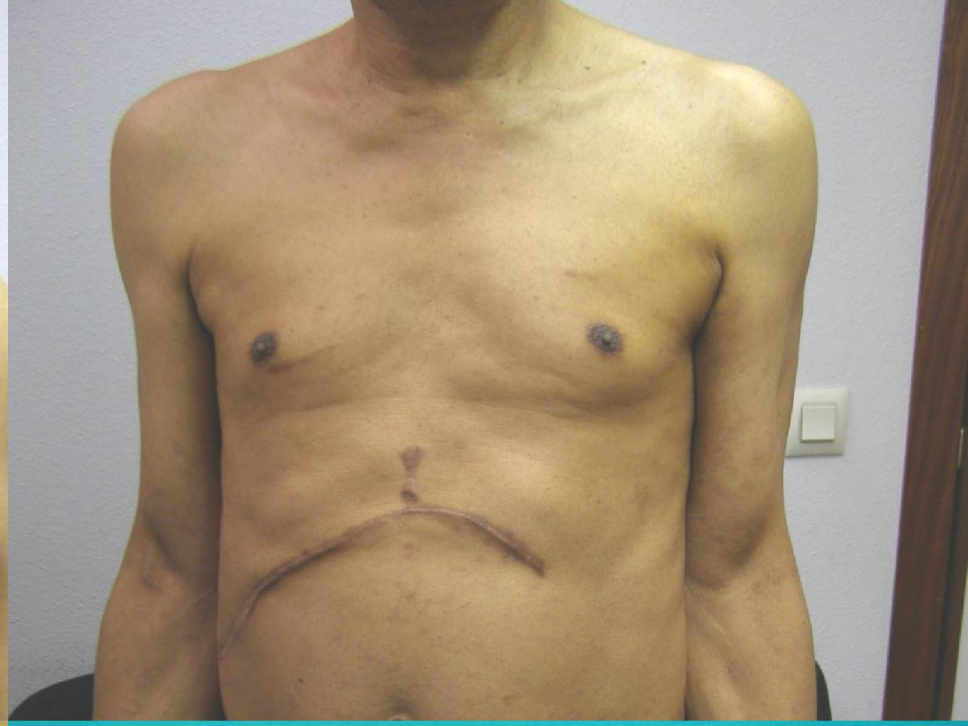
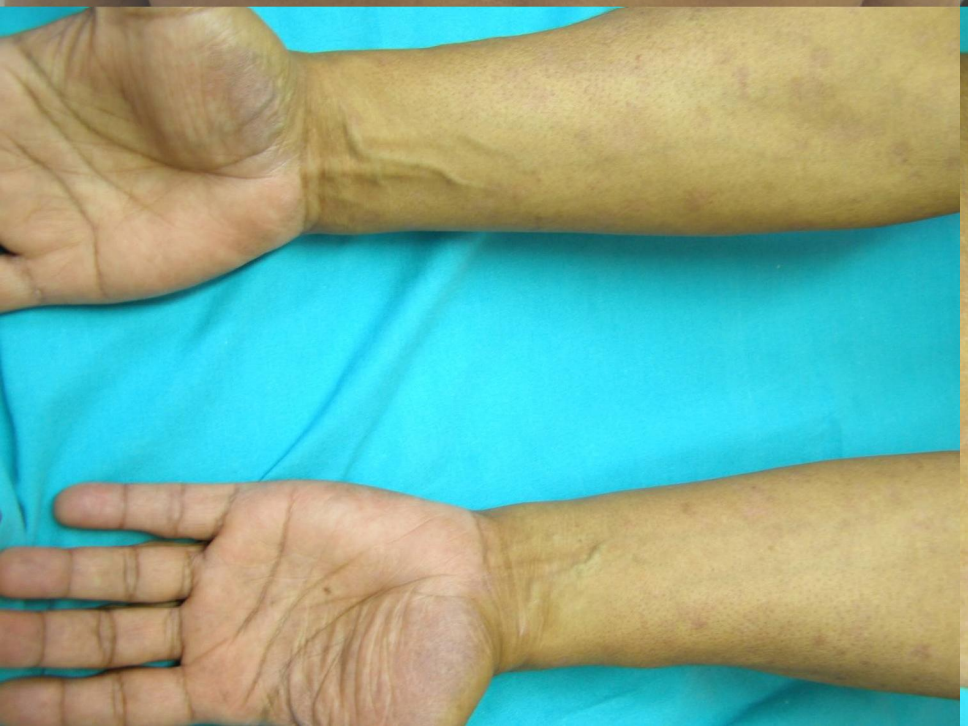
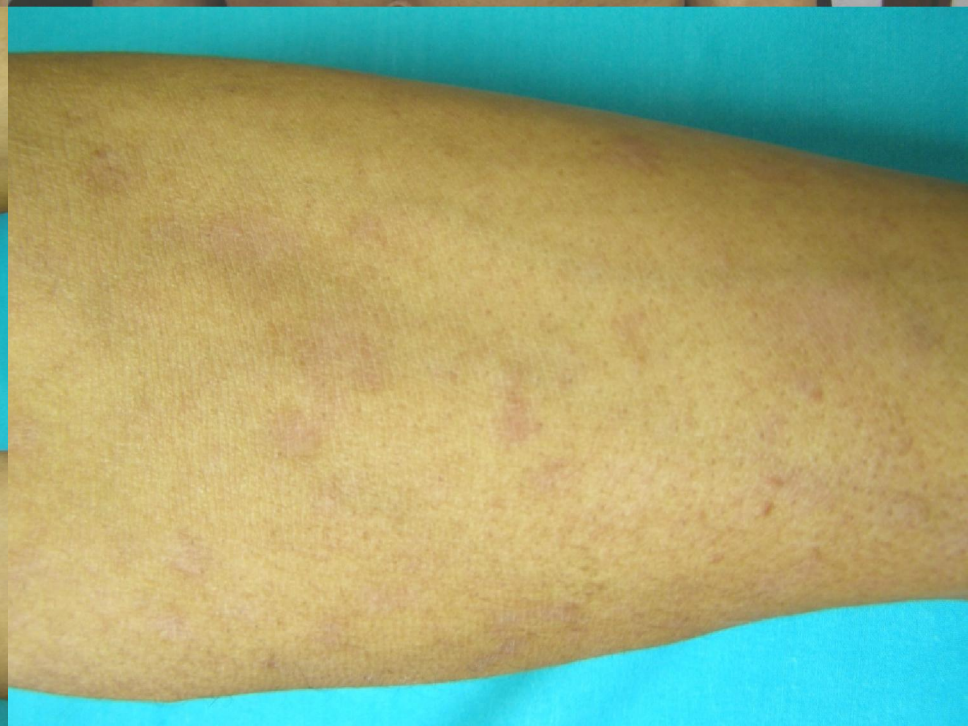


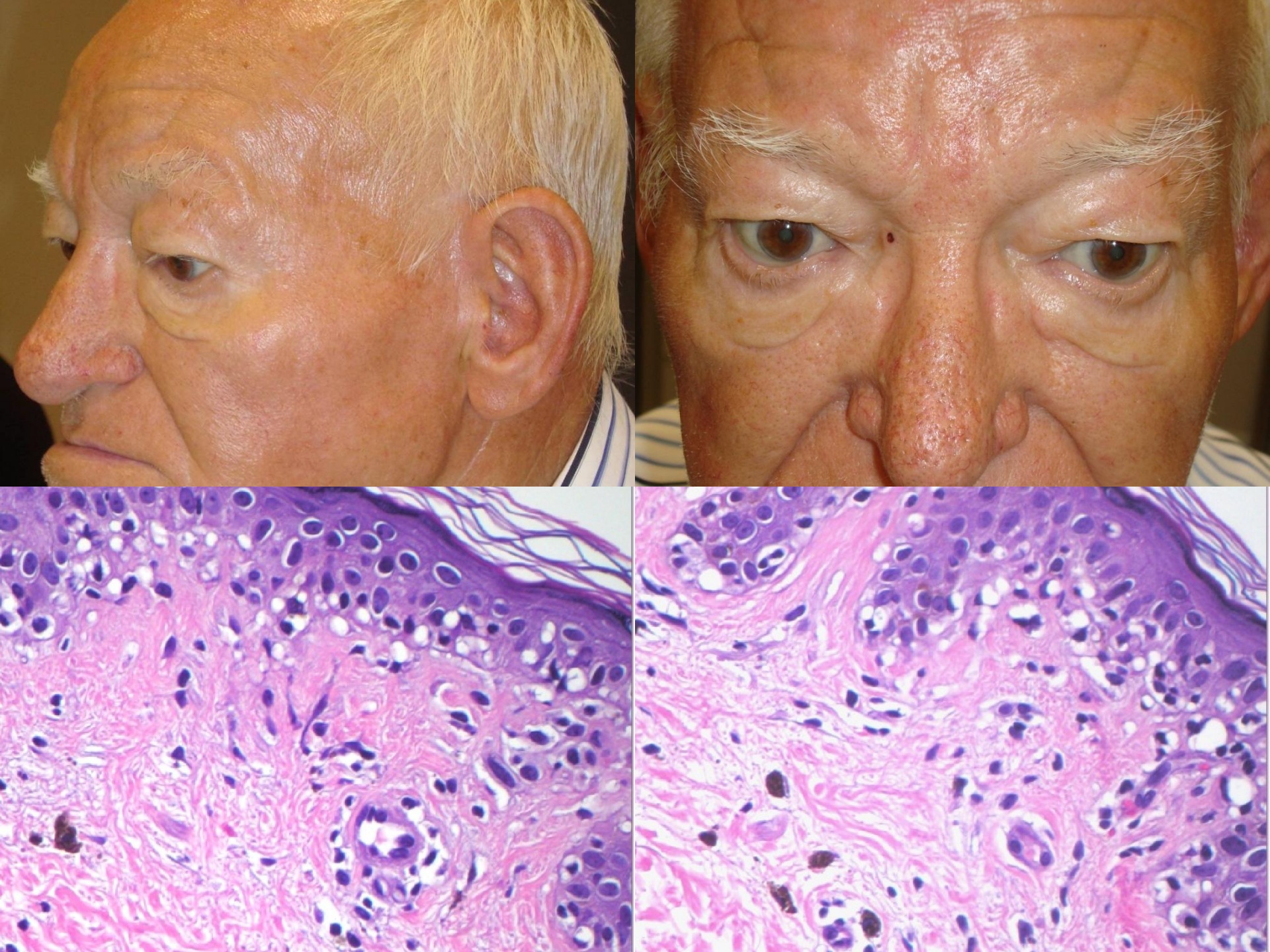


YELLOWISH DISCOLORATION OF THE SKIN

- Only described with sunitinib
- Transient yellow skin discoloration with associated yellow discoloration of urine
- Due to drug deposition in the skin and urine excretion
- Seen in 1/3 of patients
- It is noted after 1 week of treatment

J Clin Oncol 2006; 24:25-35



NEUTROPHILIC DERMATOSIS

- Pyoderma gangrenosum, Sweet syndrome, Exantematous pustulosis and neutrophilic eccrine hidradenitis
- Described with imatinib and sunitinib
- Inhibition of c-kit and PDGFR by both sunitinib and imantinib might account for the occurrence of similar cutaneous side-effects.

disorders of the central nervous system. Clin Chem 1988; 34:1387–91.

9 Sung CO, Ko YH, Park S et al. Immunoreactivity of CD99 in non-Hodgkin's lymphoma: unexpected frequent expression in ALK-positive anaplastic large cell lymphoma. J Korean Med Sci 2005; 20:952–6.

Key words: anaplastic large cell lymphoma, Ewing sarcoma, translocation

Conflicts of interest: none declared.

M.S. and R.R. contributed equally to this study.

Pyoderma gangrenosum: another cutaneous side-effect of sunitinib?

DOI: 10.1111/j.1365-2133.2008.08599.x

SIR, Pyoderma gangrenosum (PG) is a rare, noninfectious, reactive neutrophilic dermatosis which usually begins with pustules or bullae and rapidly evolves to painful ulcers with violaceous borders.[1] Histopathology reveals only nonspecific changes. However, early PG can show a perivascular and intramural lymphocytic infiltration with a peripheral neutrophilic component and fibrinoid necrosis.[1] The underlying pathogenic mechanisms remain unclear. Immune deregulation was proposed, including neutrophil dysfunction and overexpression of

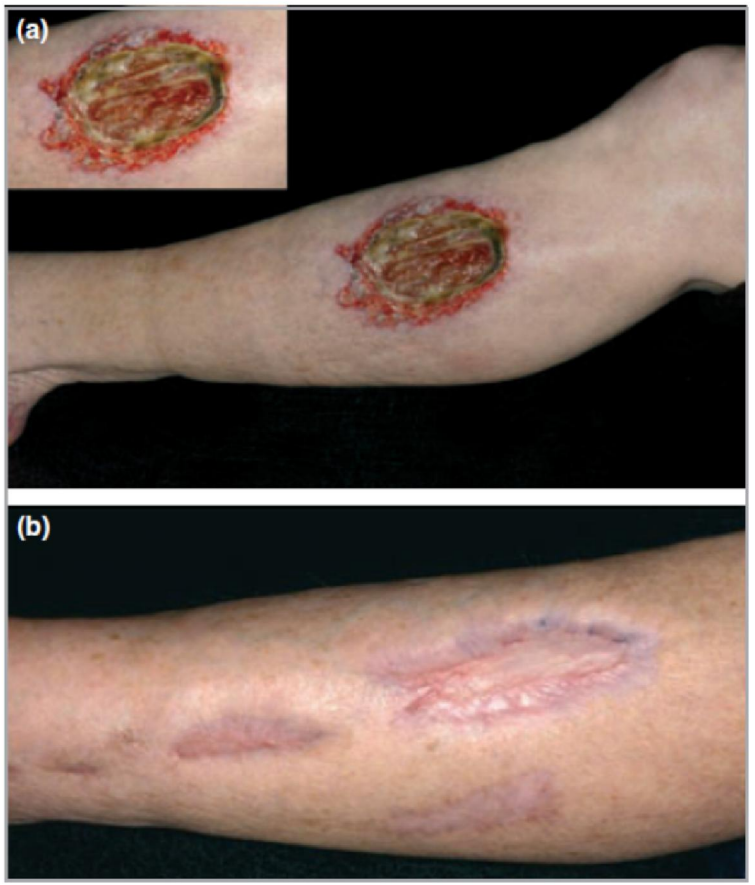
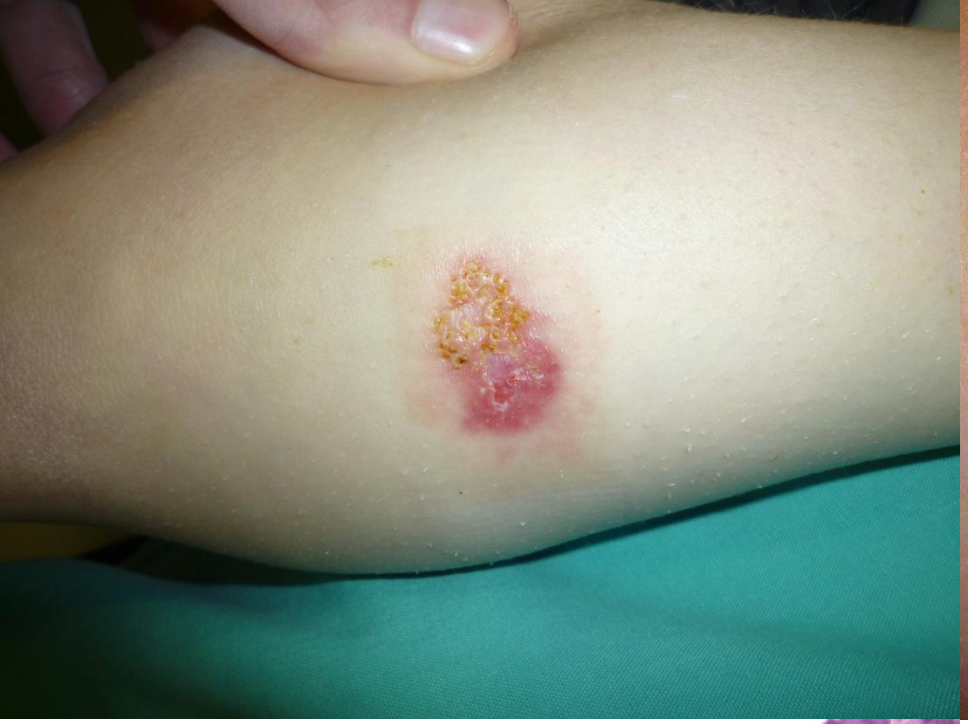
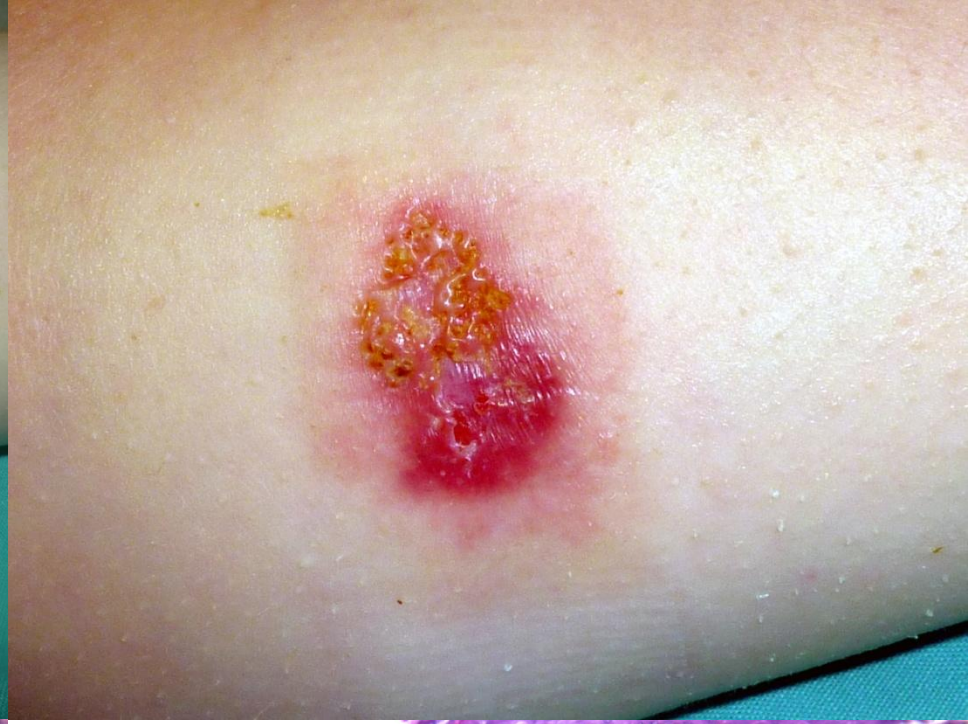
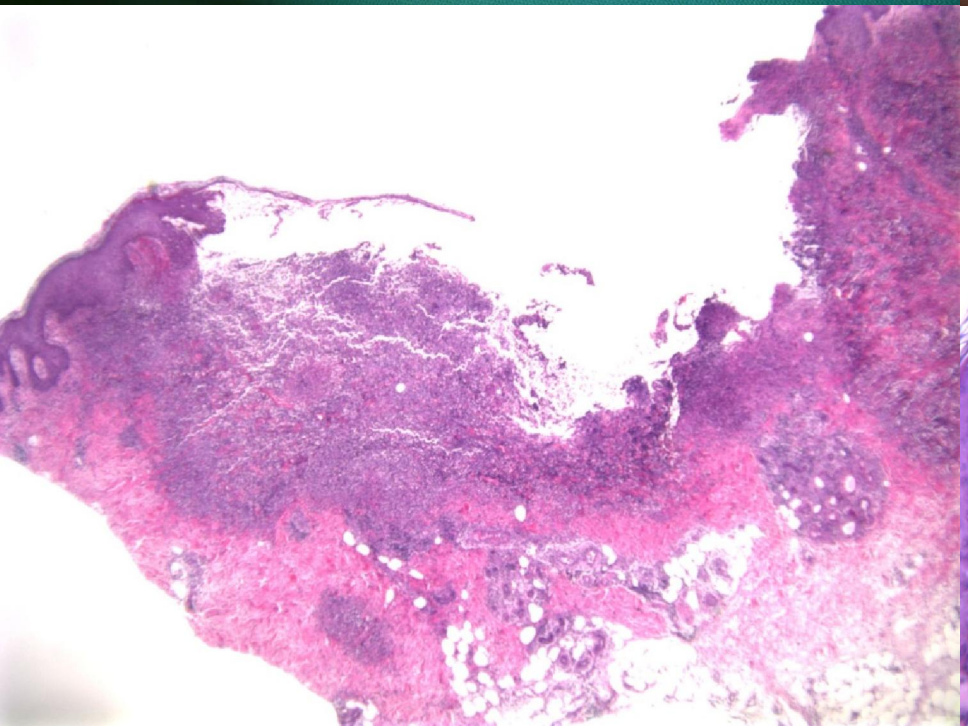
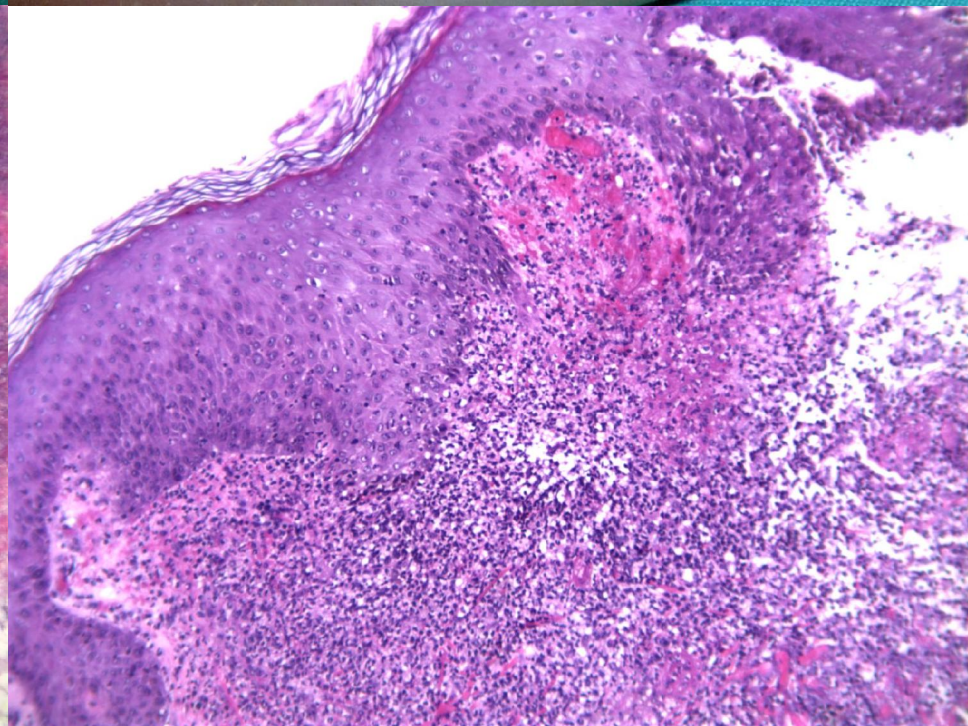


Fig 1. (a) A 76-year-old woman on sunitinib therapy presenting with a 10 × 10 cm ulcer with a green-necrotic base and an undermined violaceous border on her lower left leg after trauma. (b) Complete healing of the lesions after discontinuation of sunitinib treatment.

DRUG INDUCED PYODERMA GANGRENOSUM

- Otherwise classical PG lesions clinically
- Typically desribed with IFN, colony stimulating factors, sulpride (antipsychotic agent)
- Histologically indistinguishable from PG of idiopathic type

Crowson, Mihm , Magro. J Cutan Pathol 2003;1:30:97-107

OBSERVATION

Imatinib-Induced Sweet Syndrome in a Patient With Chronic Myeloid Leukemia

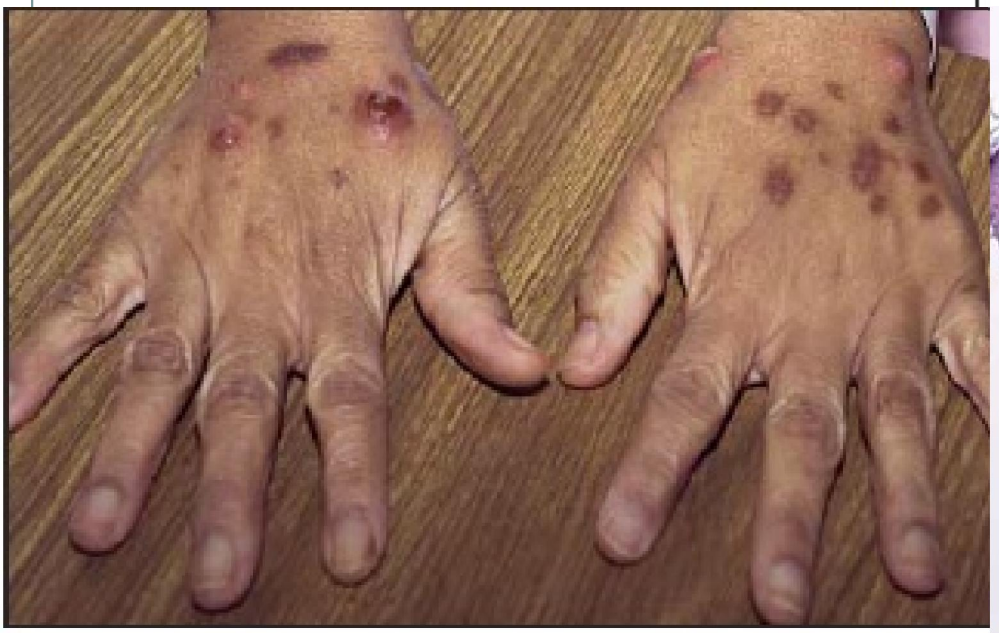
Sanjay J. Ayirookuzhi, MD; Li Ma, MD; Priya Ramshesh, MD; Glenn Mills, MD

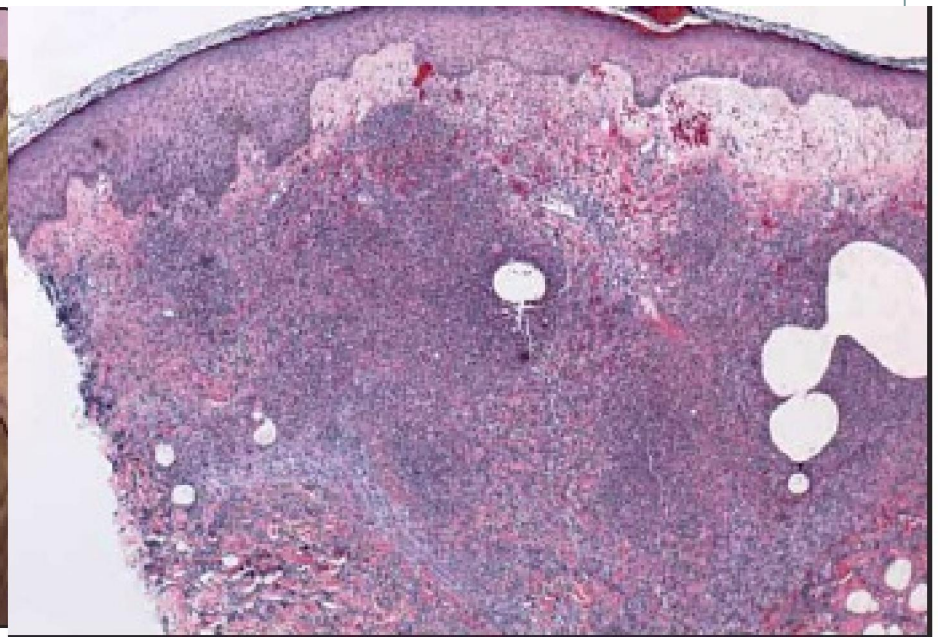
Background: Imatinib mesylate has become one of the main chemotherapeutic agents currently used to treat patients with chronic myeloid leukemia (CML). Although cutaneous reactions to this drug have been documented before, this is the first time that Sweet syndrome has been reported with its use.

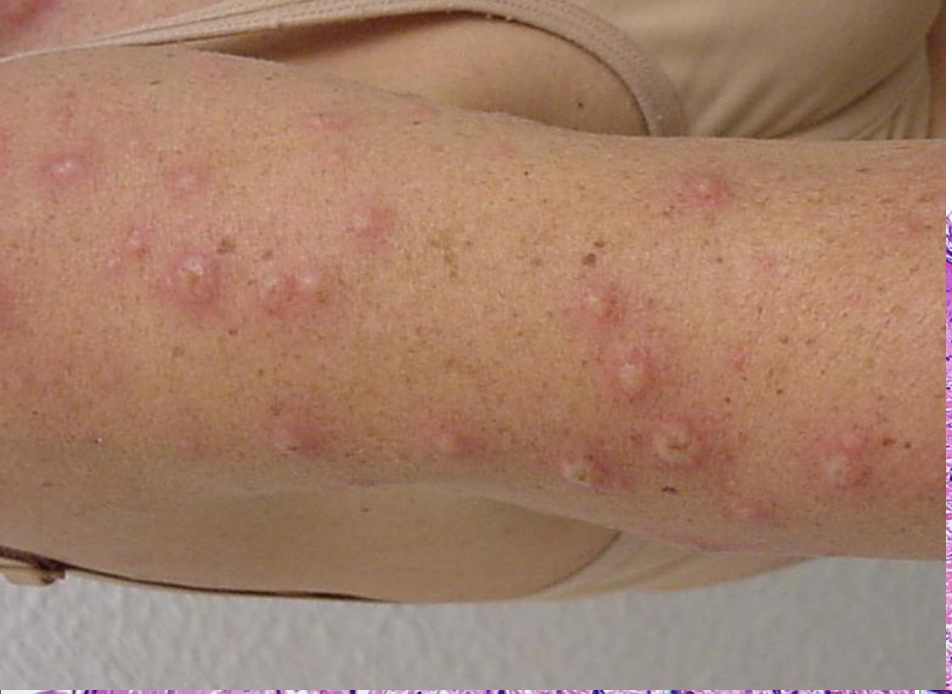
Observations: We report a case of Sweet syndrome secondary to the administration of imatinib to treat CML. On 2 separate occasions, a 53-year-old African American woman with CML developed neutrophilic dermatosis consistent with Sweet syndrome after chemotherapy with imatinib.

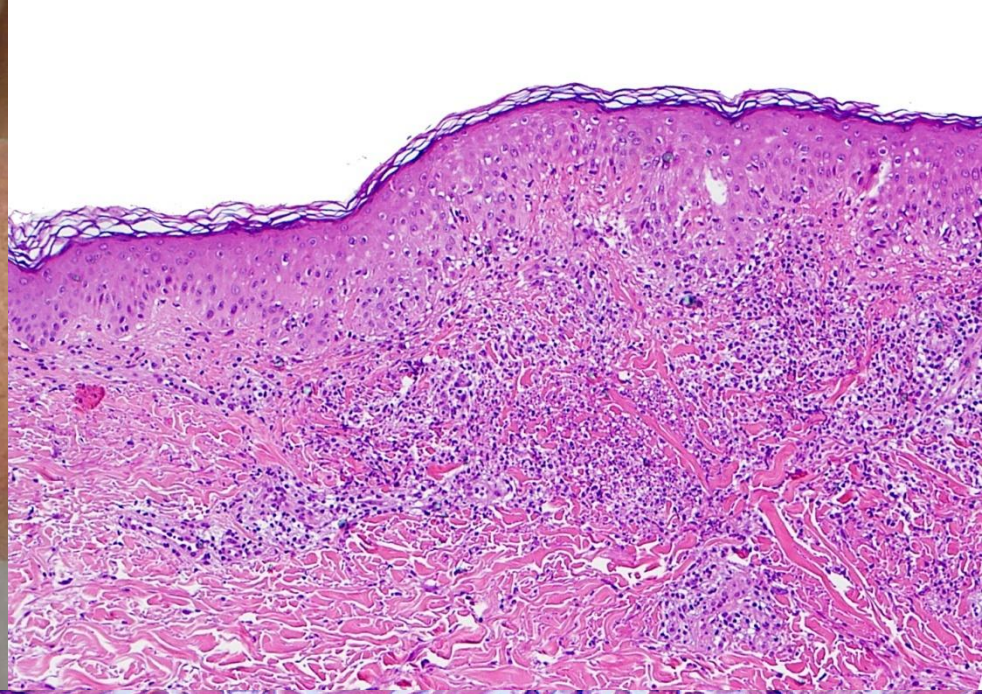
Conclusion: Greater awareness of the adverse effects of imatinib and the characterization of its cutaneous adverse effects will lead to improved surveillance for and treatment of those adverse effects.

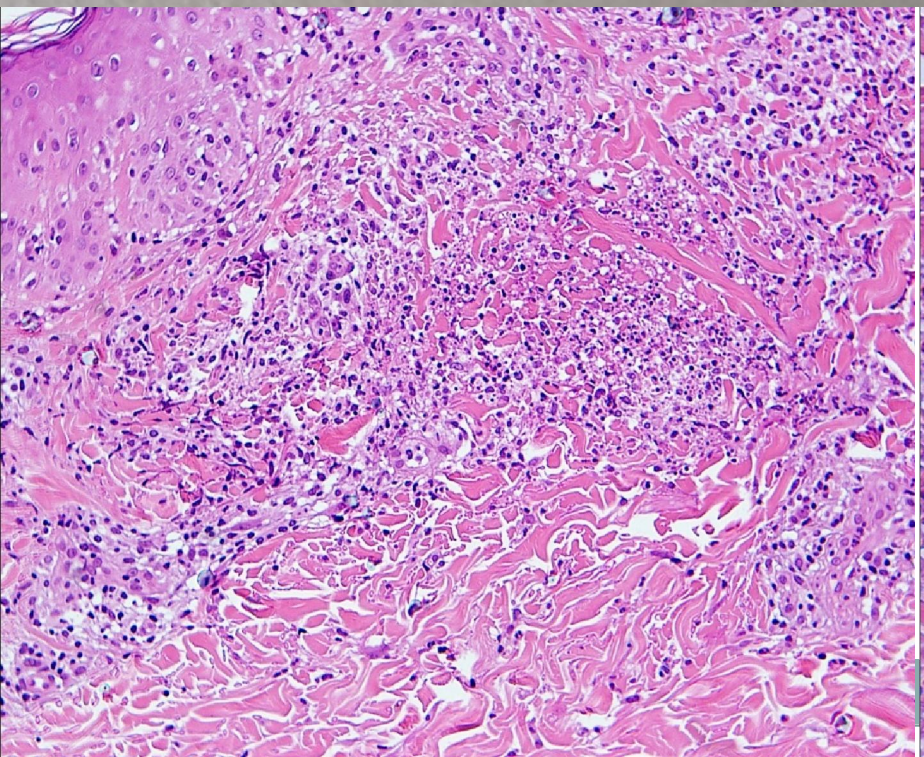
Arch Dermatol. 2005;141:368-370

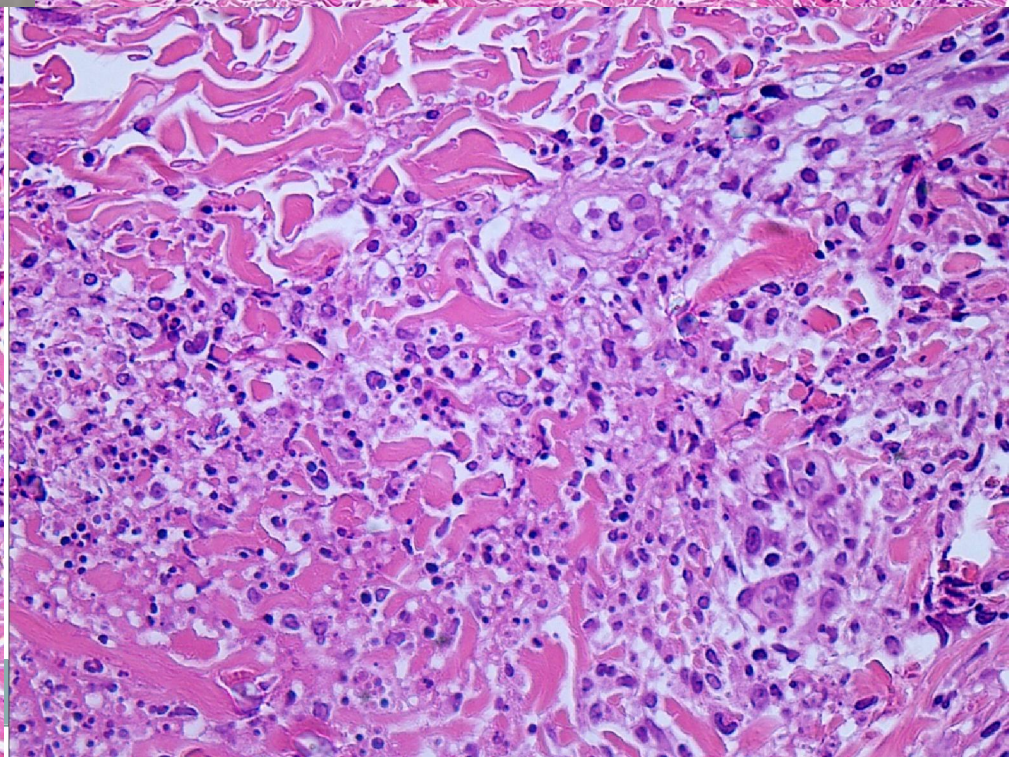












DRUG-INDUCED SWEET'S SYNDROME

- Acral-based often symmetrical pustulopapular eruption on dorsal aspect of extremities
- Typically described with Cytokines of GM-CSF/G-CSF classes
- Histologically indistinguishable from idiopathic Sweet's syndrome

OBSERVATION

Multiple Squamous Cell Carcinomas of the Skin After Therapy With Sorafenib Combined With Tipifarnib

David S. Hong, MD; Srini B. Reddy, MD; Victor G. Prieto, MD; John J. Wright, MD, PhD; Nizar M. Tannir, MD; Philip R. Cohen, MD; A. Hafeez Diwan, MD, PhD; Harry L. Evans, MD; Razelle Kurzrock, MD

Arch Dermatol. 2008;144(6):779-782

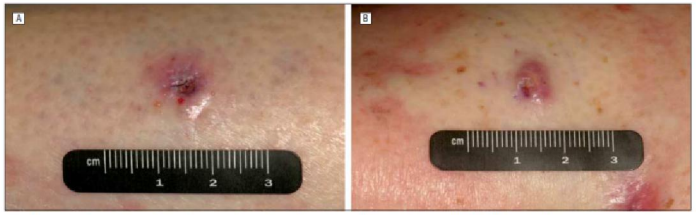


Figure 1. Erythematous nodules on the medial aspect of the right calf (A) and the right anterior thigh area (B). The picture of the lesion on the right calf was taken after biopsy.