The broad world of eosinophilic dermatoses

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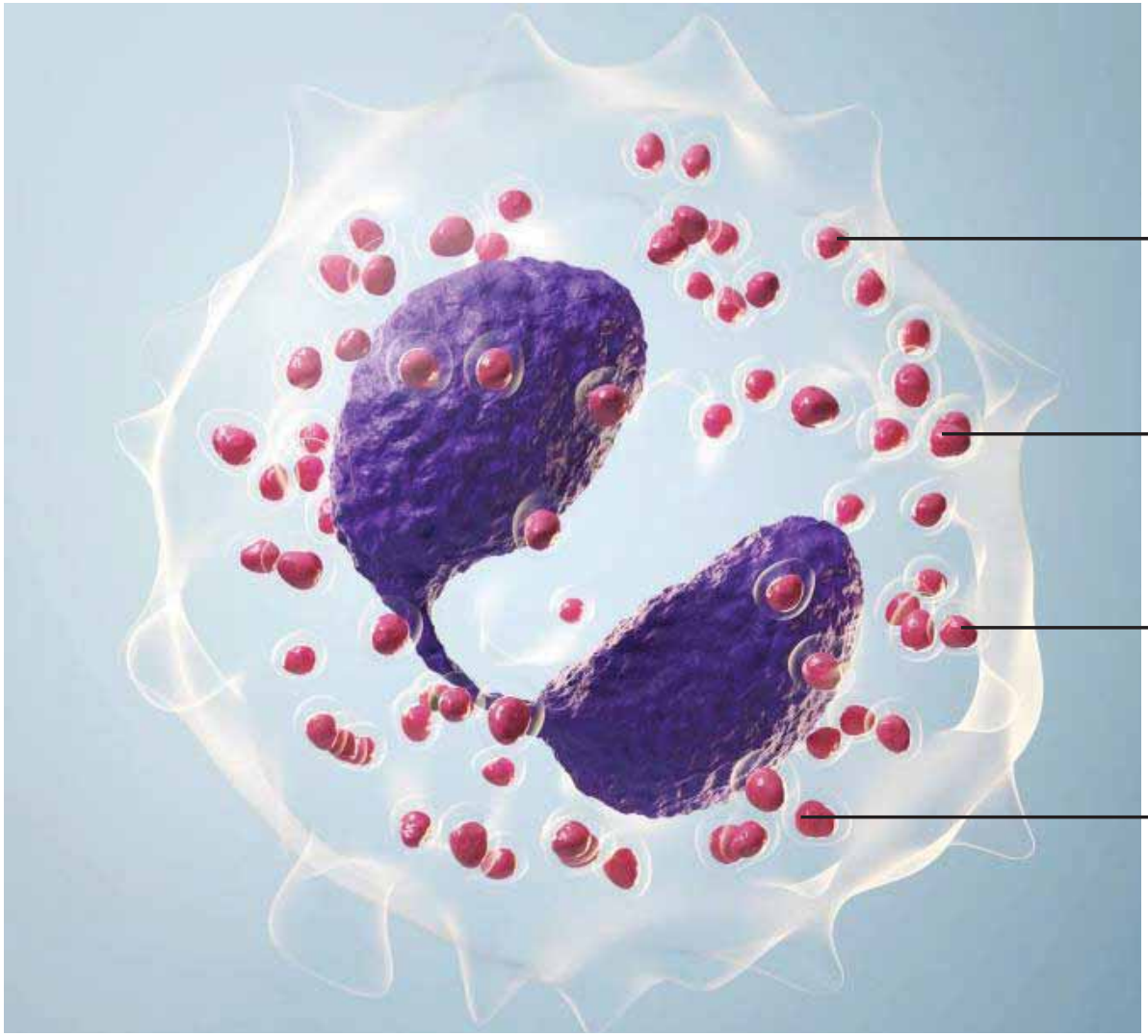
Fundación Jiménez Díaz, Universidad Autónoma,
Madrid, Spain



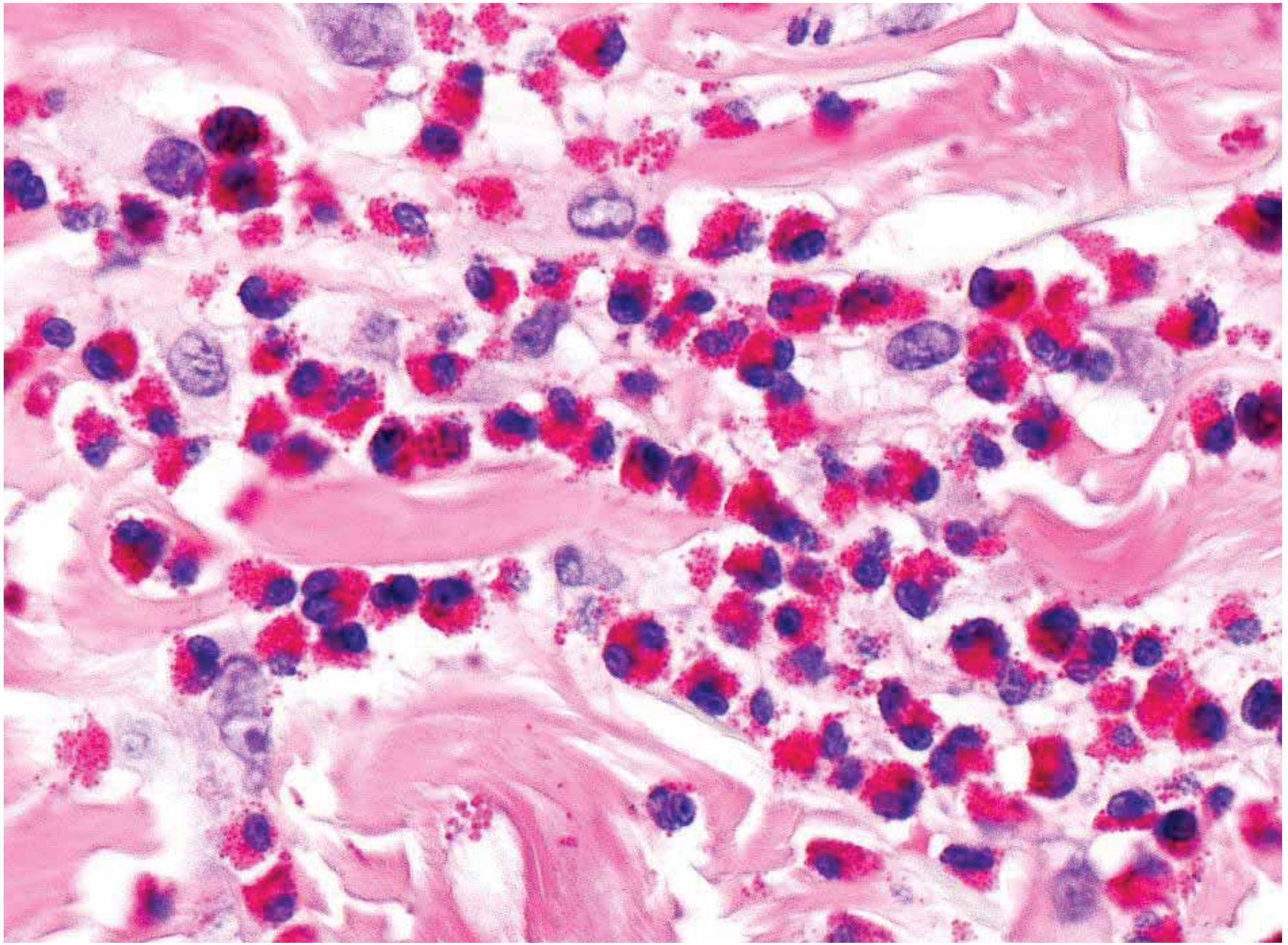
Eosinophil major basic protein 1 (EMBP1)

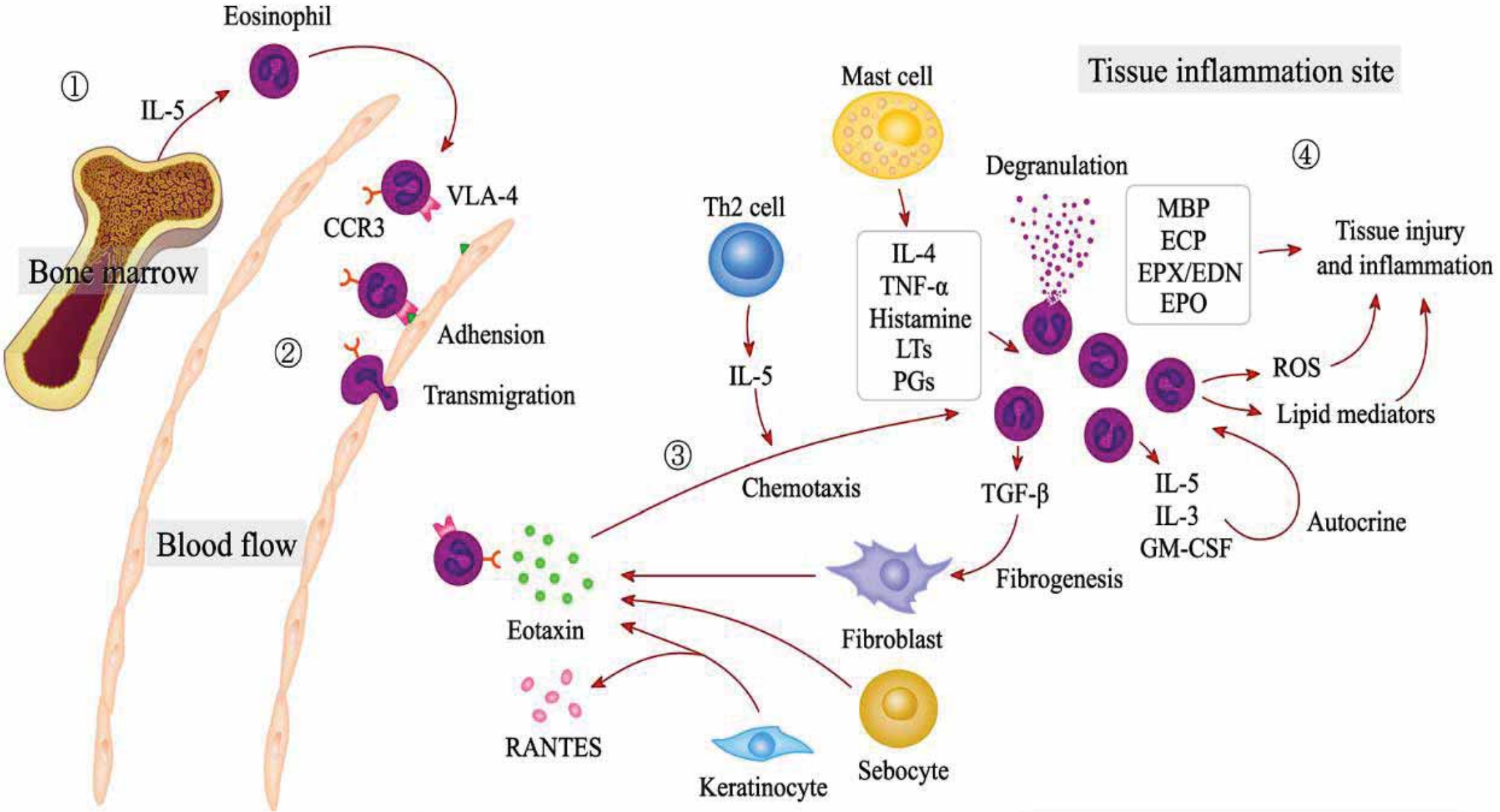
Eosinophil peroxidase (EPO)

Eosinophil protein X/eosinophil derived neurotoxin (EPX/EDN)

Eosinophil cationic protein (ECP)

Cytokines: IL-1α, TGF-α, TGF-β, IL-3, IL-5, IL-6, IL-8, TNF, GM-CSF




Eosinophil
①
IL-5
Bone marrow
VLA-4
CCR3
②
Adhension
Transmigration
Blood flow
Th2 cell
IL-5
③
Chemotaxis
Mast cell
IL-4
TNF-α
Histamine
LTs
PGs
Degranulation
Tissue inflammation site
④
MBP
ECP
EPX/EDN
EPO
Tissue injury
and inflammation
ROS
Lipid mediators
IL-5
IL-3
GM-CSF
Autocrine
TGF-β
Fibrogenesis
Eotaxin
Fibroblast
RANTES
Keratinocyte
Sebocyte

Eosinophilic dermatoses. Definition

- A heterogeneous group of skin diseases characterized by eosinophil infiltration and degranulation in the skin lesions, with or without blood eosinophilia.

EOSINOPHILIC DERMATOSES

Eosinophil location	Clinical pattern	Disorder
Epidermis	Eczematous	Atopic dermatitis Contact dermatitis Cutaneous T cell lymphoma Hypereosinophilic syndrome with cutaneous manifestations Langerhans cell histiocytosis Scabies and larva migrans
Dermo-epidermal junction	Macular and papular	Drug eruption DRESS
Papillary dermis	Urticarial	Urticaria Eosinophilic cellulitis (Wells syndrome) Episodic angioedema with eosinophilia (Gleich syndrome) Polymorphic eruption of pregnancy
Subepidermal/papillary dermis and hair follicles	Blisters and pustules	Bullous pemphigoid Pemphigus Incontinentia pigmenti Eosinophilic pustular folliculitis Erythema toxicum neonatorum
Papillary and reticular dermis	Papular and nodular	Insect bite Prurigo nodularis Eosinophilic annular erythema Eosinophilic cellulitis (Wells syndrome) Angiolymphoid hyperplasia with eosinophilia and Kimura disease Eosinophilic dermatosis associated with hematologic malignancy Primary cutaneous CD30+ lymphoproliferative disorders
Subcutis	Panniculitic	Erythema nodosum Parasitic panniculitis
Superficial vascular dermal plexus	Vasculitic	Eosinophilic vasculitis Granuloma faciale Eosinophilic granulomatosis with polyangiitis
Fascia	Fibrosis and sclerosis	Localized scleroderma Systemic sclerosis Eosinophilic fasciitis

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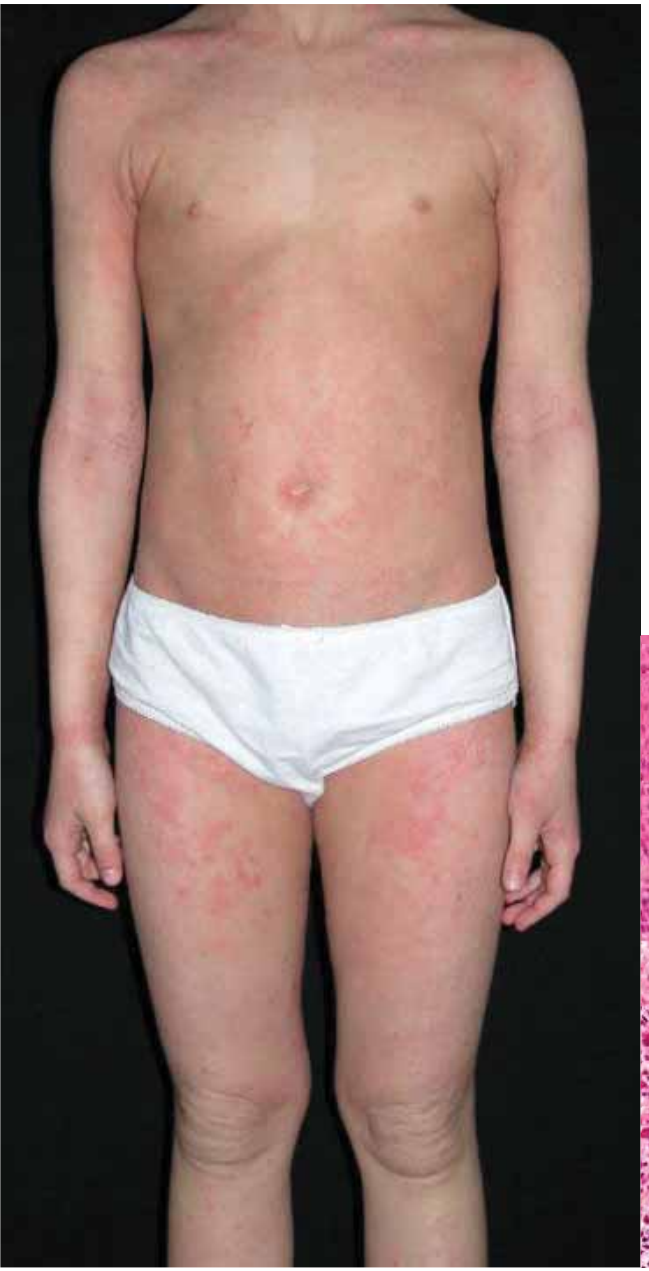

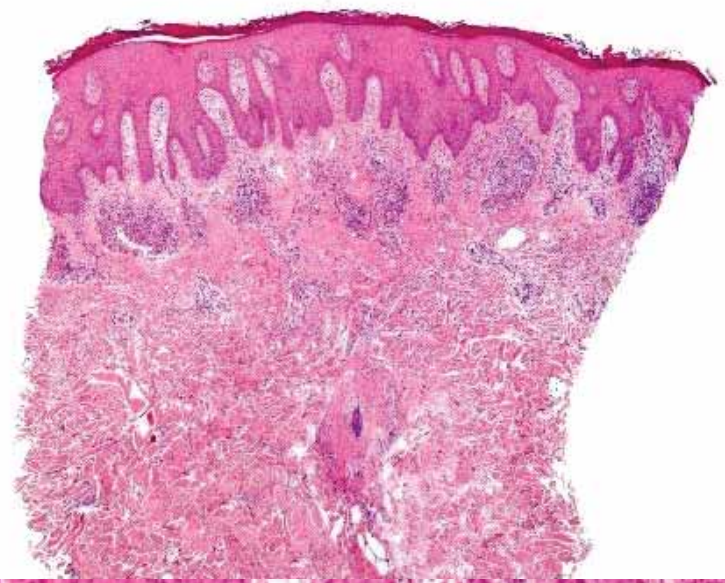

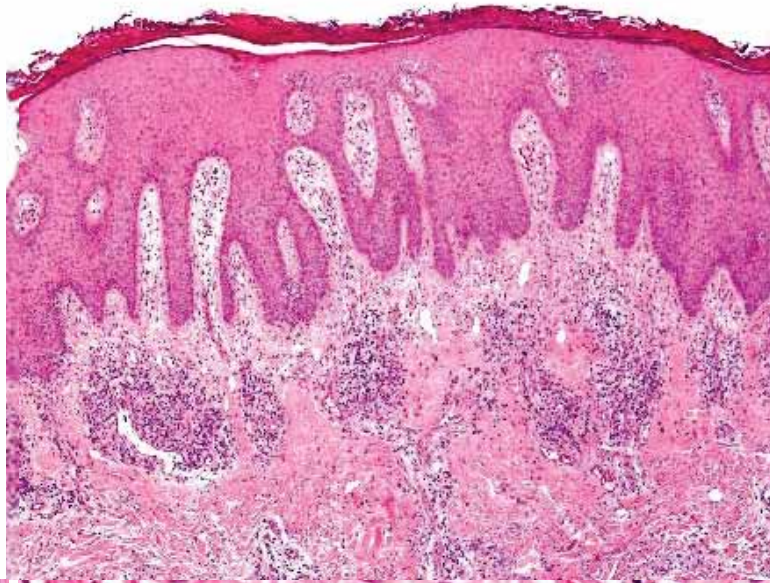

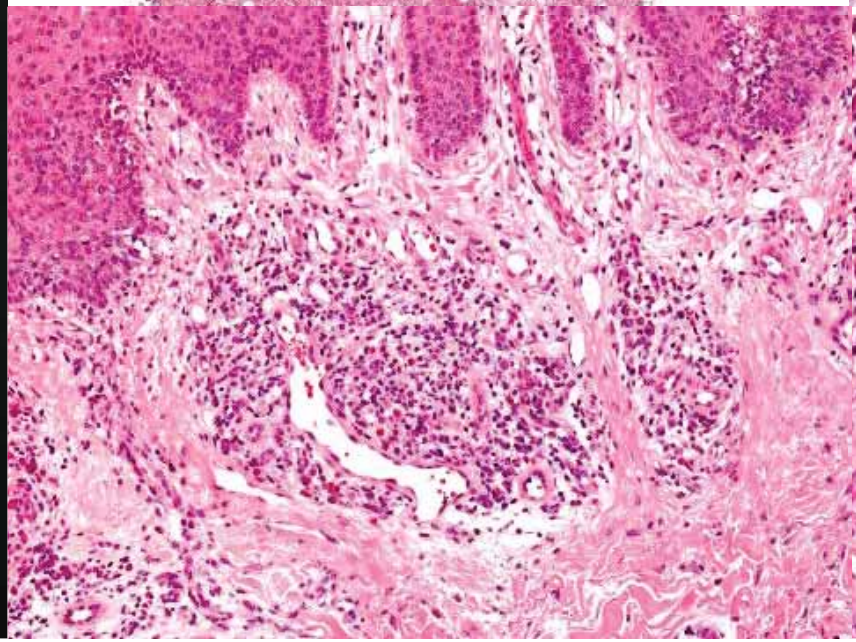

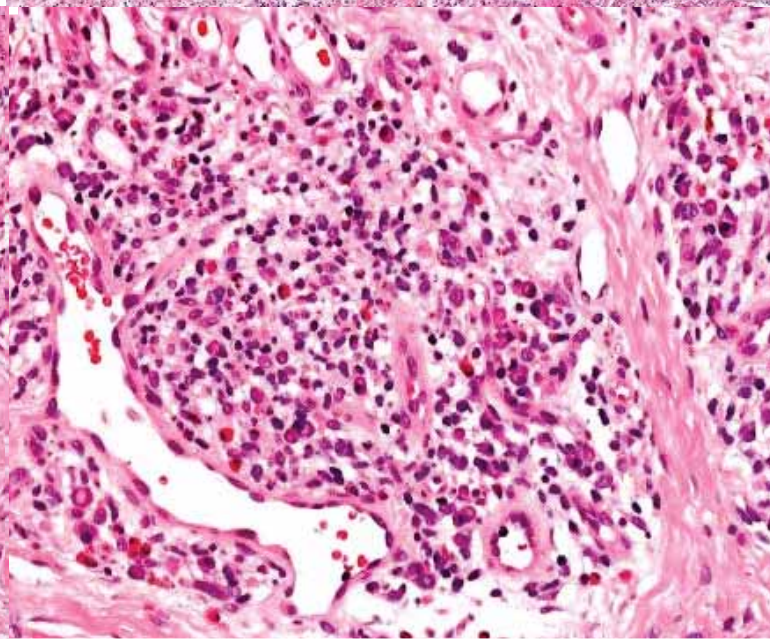

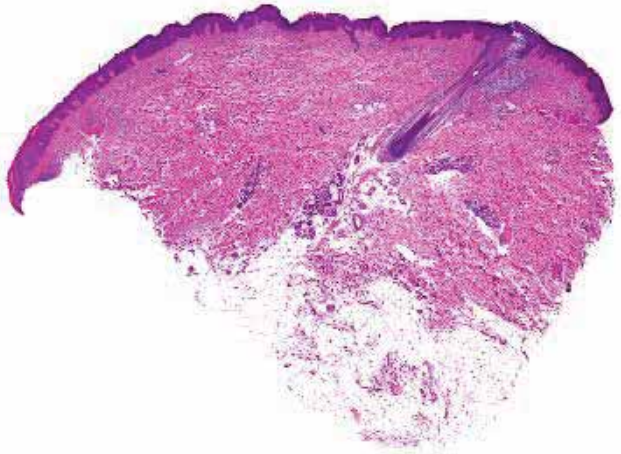
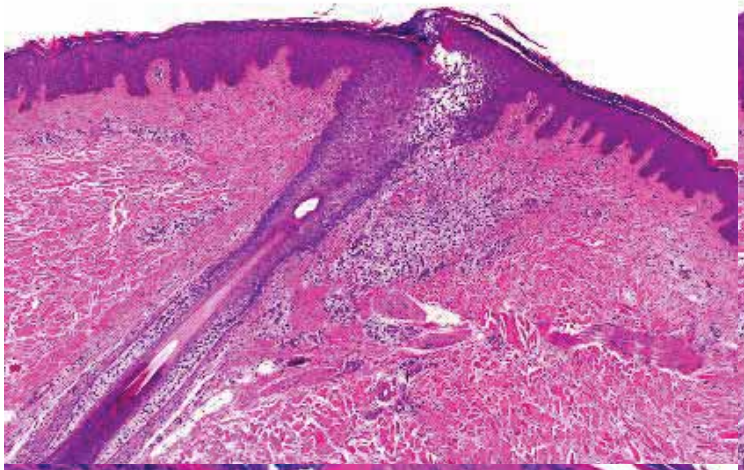
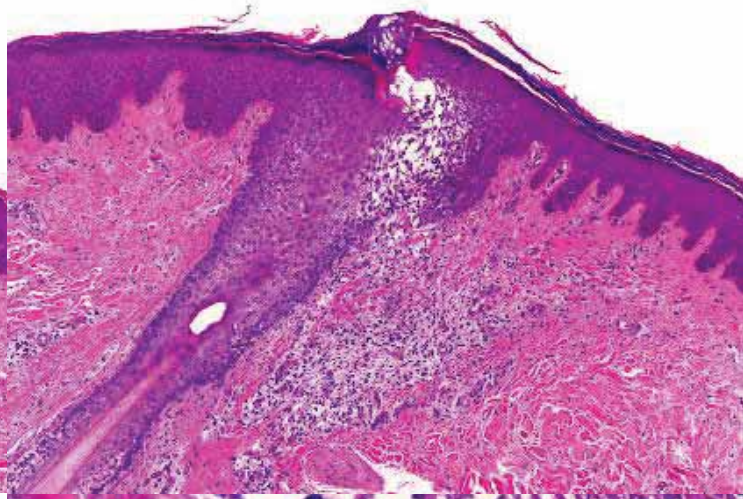
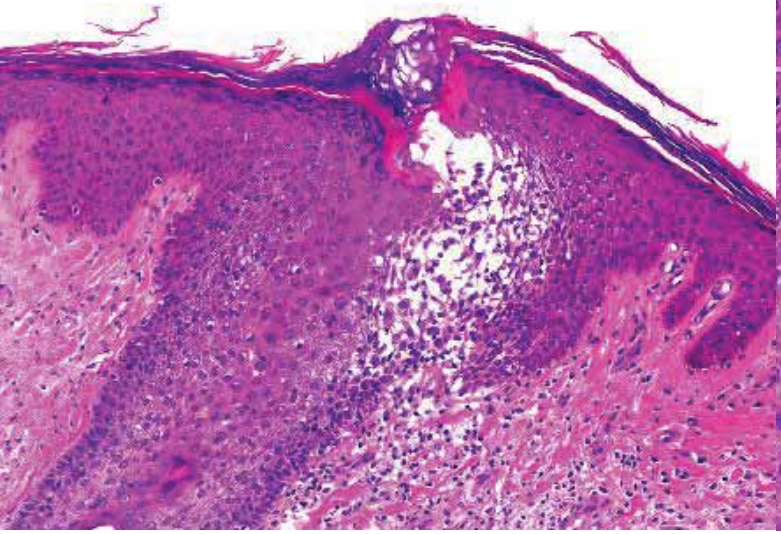
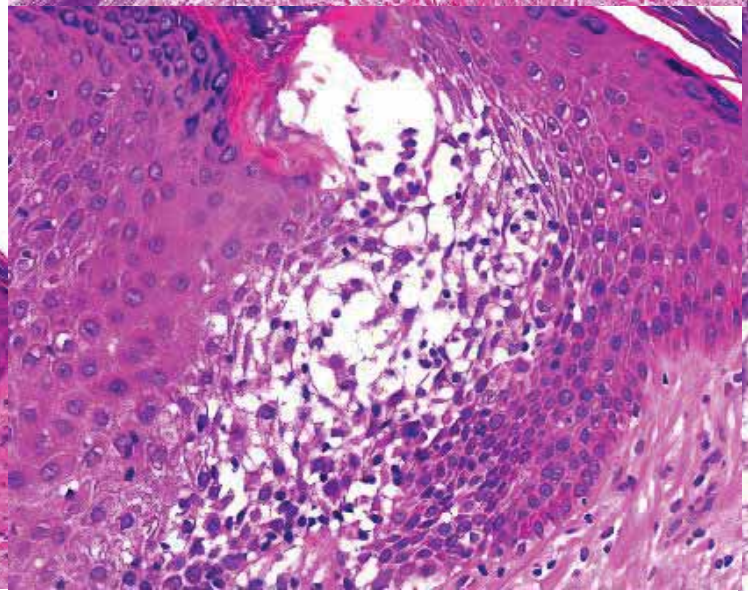
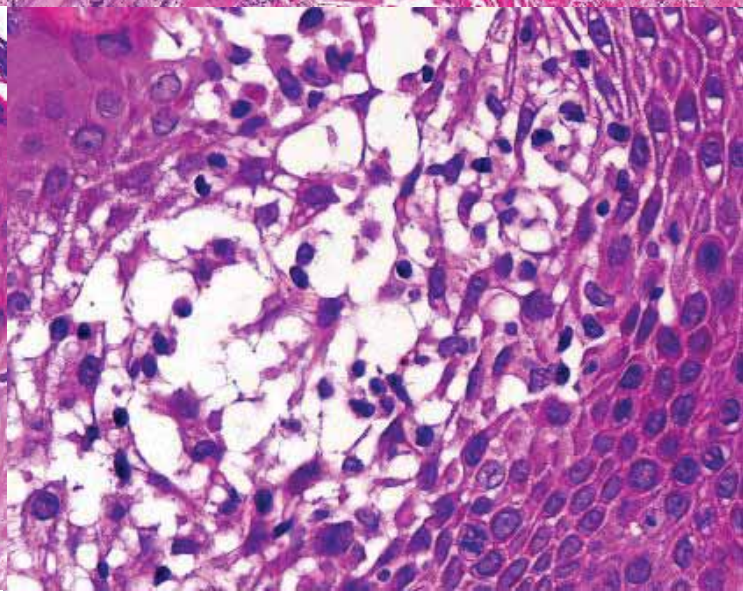

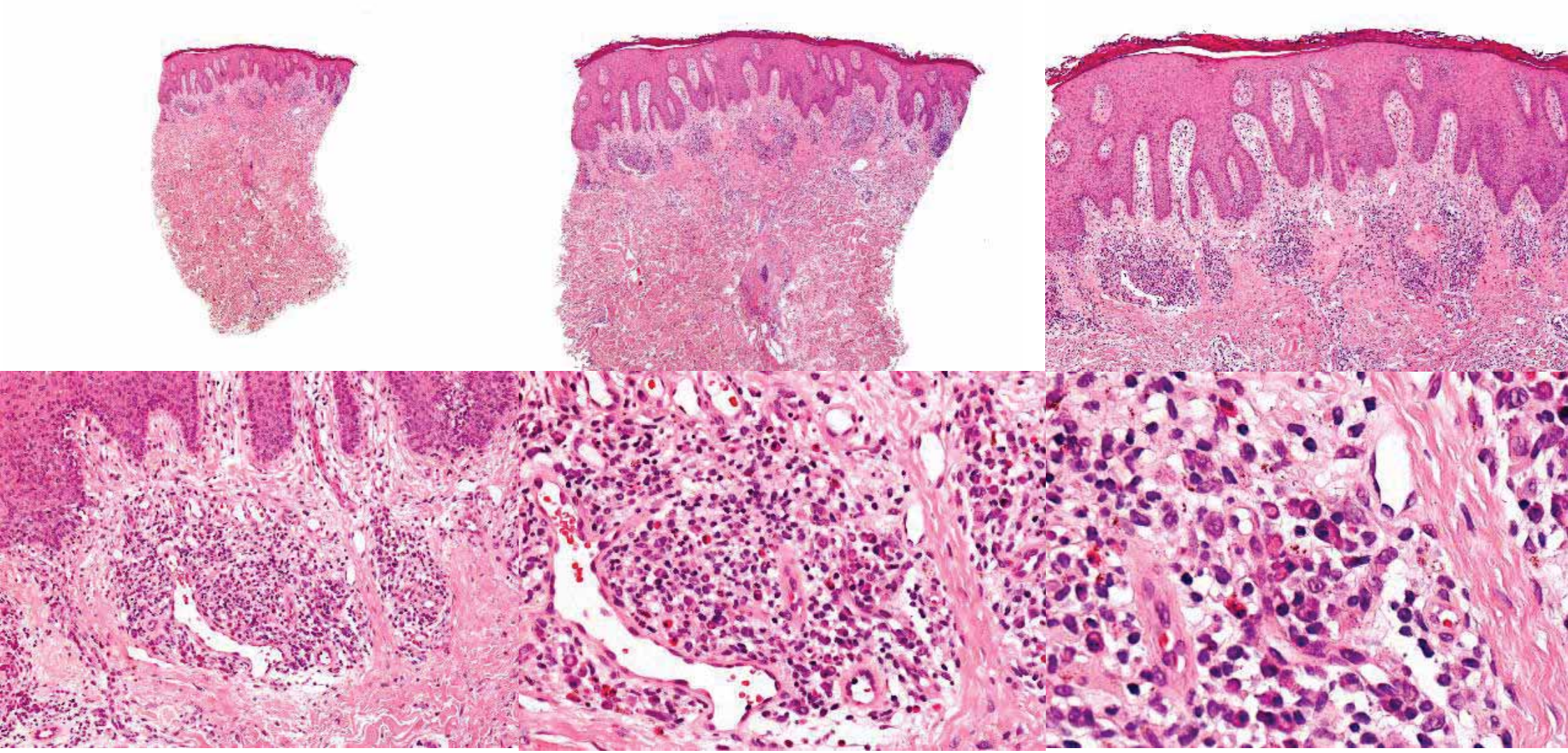

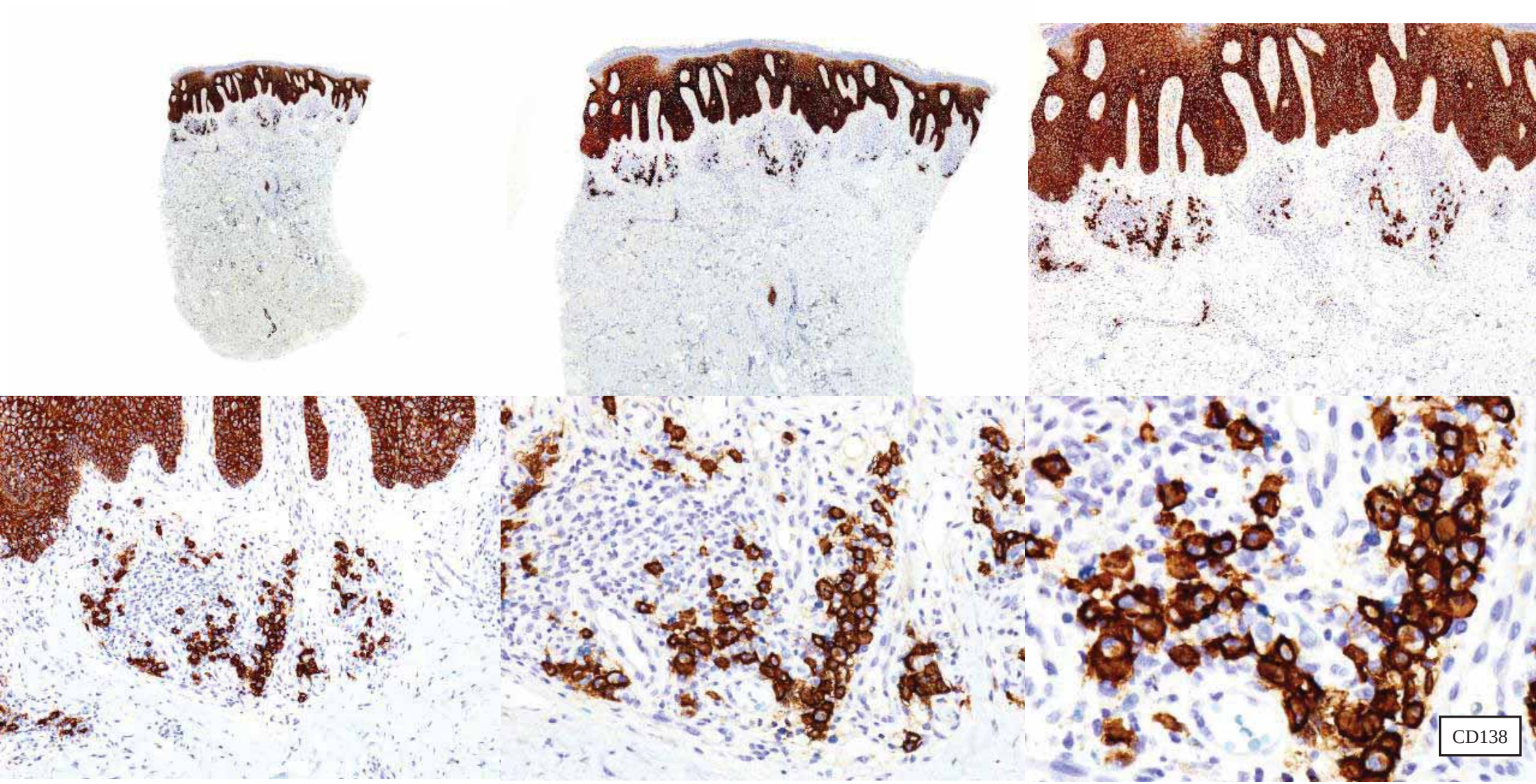
CD138

Clue

- Plasma cells in the inflammatory infiltrate of atopic dermatitis is a clue to atopic dermatitis under treatment with Dupilumab.

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Fifth Edition

DERMATOLOGY

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ELSEVIER

DIAGNOSTIC CRITERIA AND CLASSIFICATION OF HYPEREOSINOPHILIC SYNDROMES (HESs) AND OTHER ENTITIES WITH HYPEREOSINOPHILIA

Three diagnostic criteria

1. Peripheral blood hypereosinophilia – defined as >1.5 eosinophils $\times 10^9$/L blood [>1500 eosinophils/mcl]* on two examinations at an interval of one month or greater† – and/or –
   Tissue hypereosinophilia defined by the following:
   - Percentage of eosinophils in bone marrow section exceeds 20% of all nucleated cells
     – and/or –
   - Pathologist is of the opinion that tissue infiltration by eosinophils is extensive
     – and/or –
   - Marked deposition of eosinophil granule proteins is found in the absence or presence of major tissue infiltration by eosinophils
2. Organ damage and/or dysfunction attributable to tissue hypereosinophilia
3. Exclusion of other disorders or conditions as major reason for organ damage

Variants of HES (end-organ damage attributable to hypereosinophilia)

Myeloid HES (MHES, neoplastic, primary) – 15%–20%	*Lymphocytic HES (LHES, secondary)*	*Overlap HES – eosinophilic disease restricted to a single organ – or – a defined eosinophilic syndrome that overlaps in clinical features with idiopathic HES*
• Underlying neoplasm of stem cells, myeloid cells, or eosinophils (WHO classification) • Eosinophils are considered (or shown) to be clonal‡ • Male predominance • In addition to typical skin lesions (see text), signs of cutaneous thromboses (e.g. retiform purpura) • Mucosal ulcers poor prognostic sign • Fever, weight loss, malaise, subendocardial fibrosis, restrictive cardiomyopathy, mitral or tricuspid valve insufficiency, hepatosplenomegaly, neutrophilia • Some patients have high serum tryptase and vitamin B_{12} levels, tissue fibrosis, splenomegaly, and bone marrow biopsies with increased numbers of $CD25^+$ atypical spindle-shaped mast cells¶	• Hypereosinophilia is thought to be cytokine-driven, due to clonal T cells§ producing Th2 cytokines (IL-5, -4, -13) • Skin is most commonly affected organ (severe pruritus, dermatitis, erythroderma, urticaria, angioedema) • Lymphadenopathy • Serum IgE and TARC (CCL17) levels are typically elevated (likely due to actions of IL-4, -13) • T cell clone often remains stable for years, but transformation to lymphoma can occur	• Episodic angioedema with eosinophilia (Gleich syndrome)‖ • Nodules, eosinophilia, rheumatism, dermatitis and swelling (NERDS) syndrome‖ • Eosinophilic granulomatosis with polyangiitis (EGPA) • Eosinophilia myalgia syndrome and toxic oil syndrome (both historic)

Associated HES (secondary, reactive)	*Overlap HES (eosinophilic disease restricted to an organ other than the skin)*
• HES in the setting of a known secondary cause • Hypereosinophilia cytokine-driven (IL-3, IL-5, GM-CSF), but not due to clonal T lymphocytes • Associated with underlying primary immunodeficiencies (e.g. Omenn syndrome, hyper IgE syndrome [*STAT3* or *DOCK8* mutations]), atopic diseases, helminth or other infections, drug hypersensitivity or other inflammatory disorders (e.g. chronic GVHD), hematologic or solid-organ malignancies • Systemic mastocytosis, including with an associated hematologic (non-mast cell lineage) neoplasm • Hypereosinophilia also seen in patients with cholesterol emboli, inflammatory bowel disease, and sarcoidosis	• Eosinophilic *gastrointestinal* diseases – eosinophilic esophagitis, gastroenteritis, colitis, pancreatitis, and hepatitis; eosinophilic ascites • Eosinophilic *pulmonary* diseases – eosinophilic asthma, bronchitis, pneumonia, pleuritis, rhinosinusitis (and nasal polyposis) • Eosinophilic *genitourinary* diseases – nephritis, cystitis, endometritis, myometritis • Other eosinophilic diseases – mastitis, myocarditis, synovitis, ocular disorders

*Eosinophilia is defined as 0.5–1.5 eosinophils $\times 10^9$/L blood.

†In the case of evolving life-threatening end-organ damage, the diagnosis of HES can be made immediately to avoid delay in treatment.

‡*FIP1L1-PDGFRA* fusion gene (>80% of patients) and other rarer fusion genes or rearrangements involving *PDGFRB*, *FGFR1* or *PCM1-JAK2*, which encode platelet-derived growth factor receptor-β, fibroblast growth factor receptor-1, and pericentriolar material 1-Janus kinase 2, respectively; includes patients with eosinophilic leukemia, who may have other cytogenetic abnormalities. Point mutations in *JAK2* may also be seen.

¶In the WHO classification of mastocytosis, such patients (who have the *FIP1L1-PDGFRA* fusion gene) are designated as having systemic mastocytosis with associated clonal hematological non-mast cell-lineage disease (SM-AHNMD).

§Some patients have phenotypically abnormal lymphocyte populations with unique surface phenotypes (e.g. $CD3^+CD4^-CD8^-$, $CD3^-CD4^+$).

‖May develop T cell clones.

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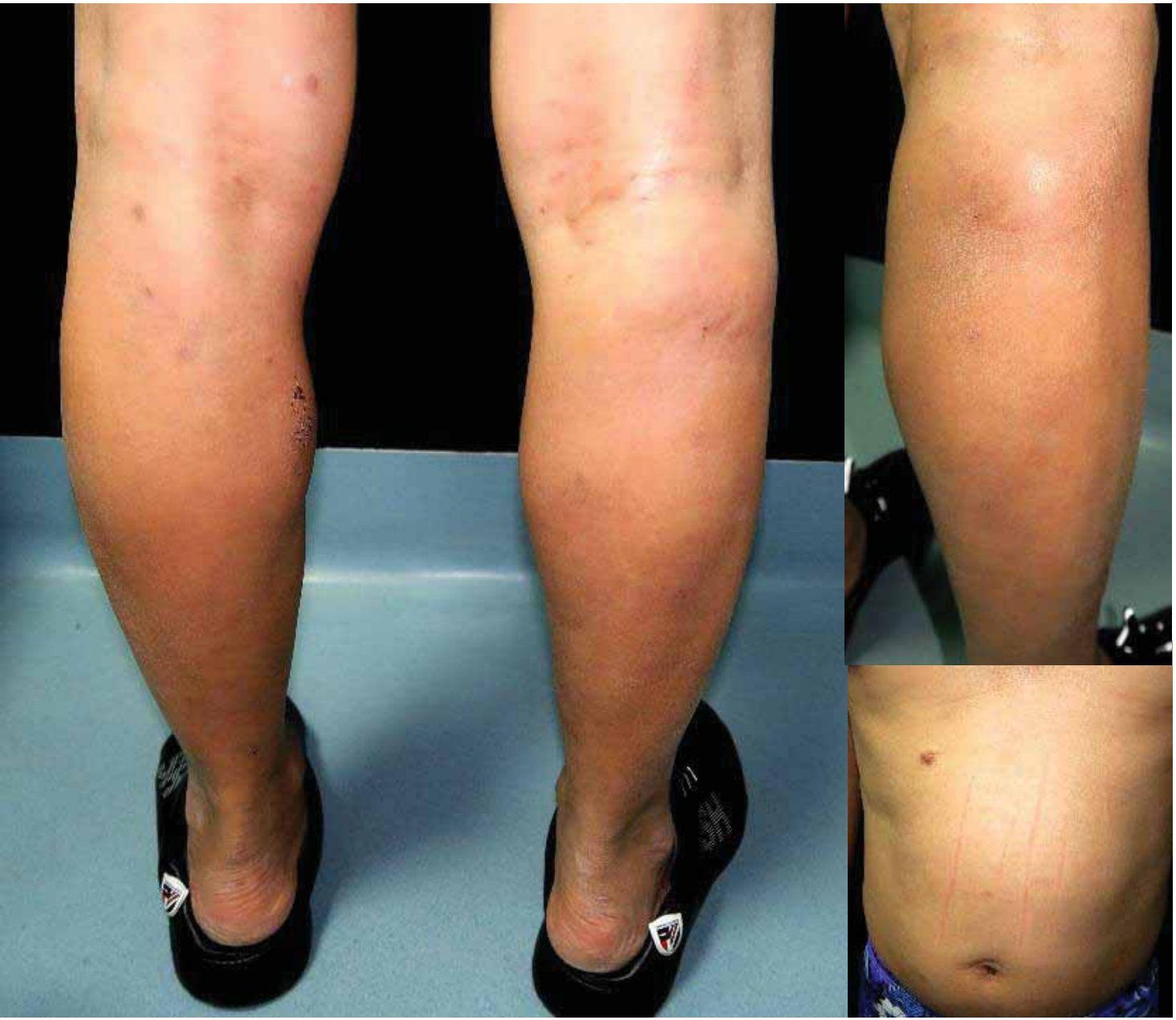
Variants of hypereosinophilic syndrome (HES)

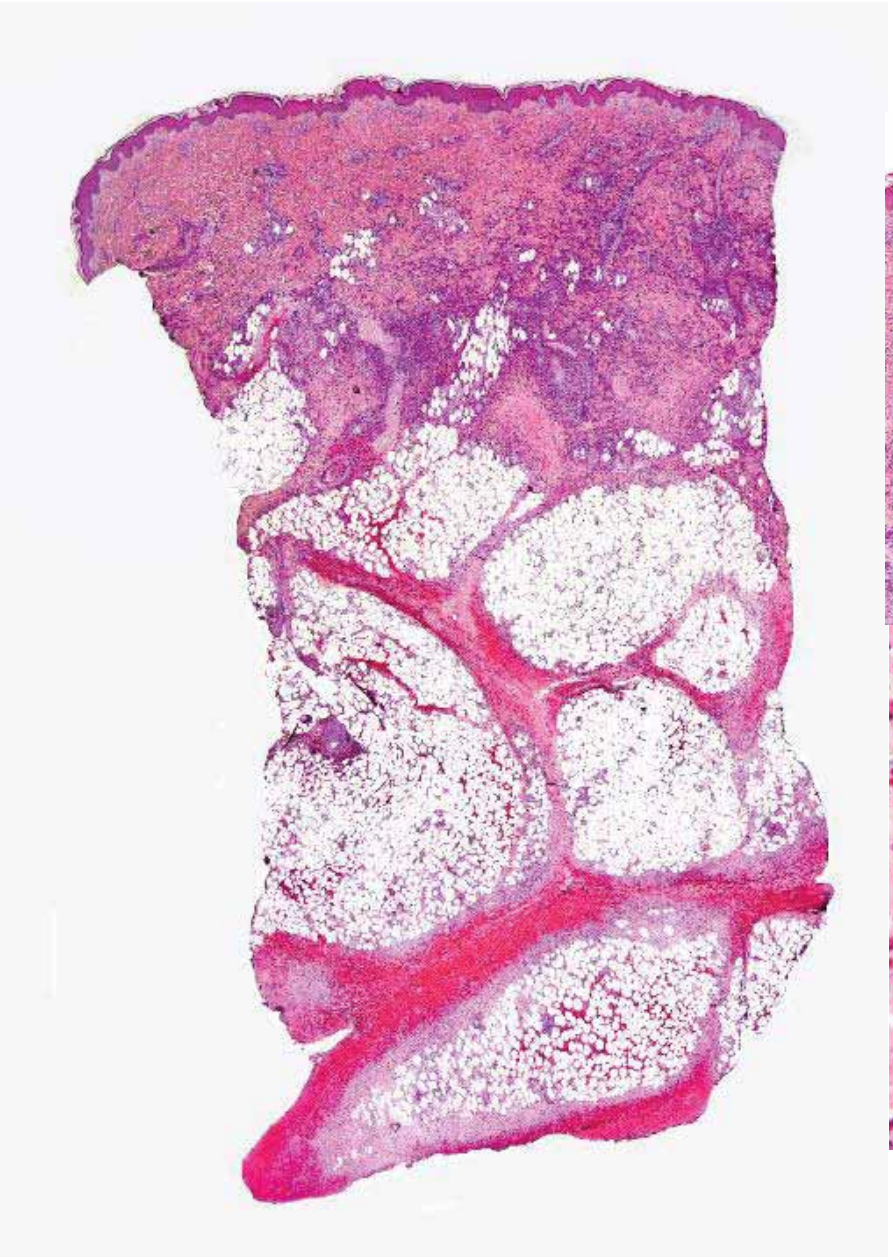
- Myeloid (MHES, neoplastic or primary):
  - Underlying neoplasm of stem cells, myeloid cells or eosinophils.
  - Eosinophils are clonal (chronic eosinophilic leukemia).
  - *FIP1L1-PDGFRA* fusion in > 80% of patients.
- Lymphoid (LHES, secondary):
  - Hypereosinophilia results from cytokine-driven due to clonal T cells producing Th2 cytokines (IL-4, -5 and -13).
  - T-cell clone usually remains stable without progression to lymphoma.
- Associated HES (secondary, reactive):
  - HES asscociated a known secondary cause.
  - Omenn syndrome, hyper IgE syndrome (*STAT3* or *DOCK8* mutations), atopic dermatitis, drug eruptions, systemic mastocytosis.
- Overlap HES-eosinophilic dermatoses:
  - Episodic angioedema with eosinophilia (Gleich syndrome).
  - ***N***odules, ***e***osinophilia, ***r***heumatism, ***d***ermatitis and ***s***welling (NERDS syndrome).
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease).

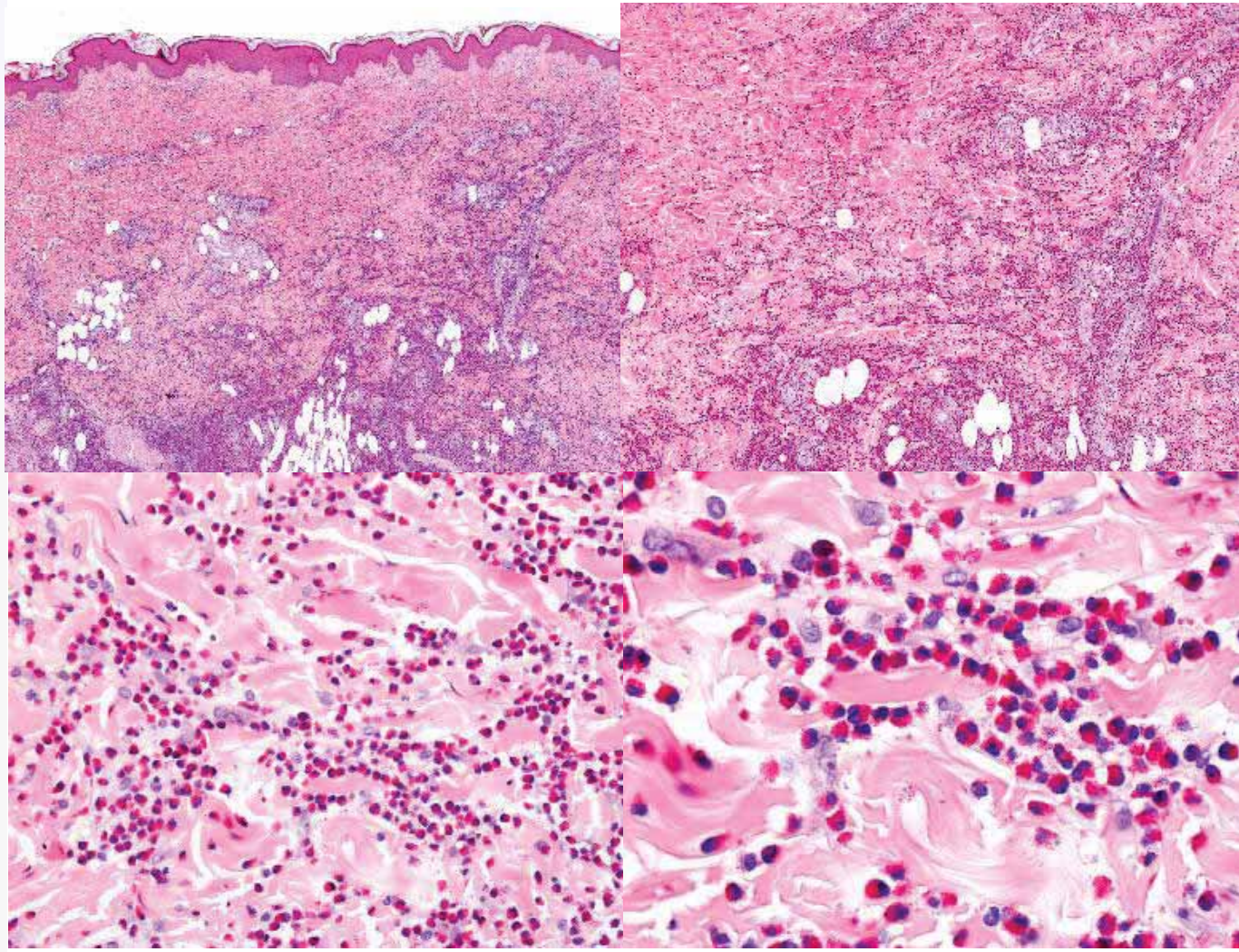
Cutaneous manifestations of hypereosinophilic syndrome

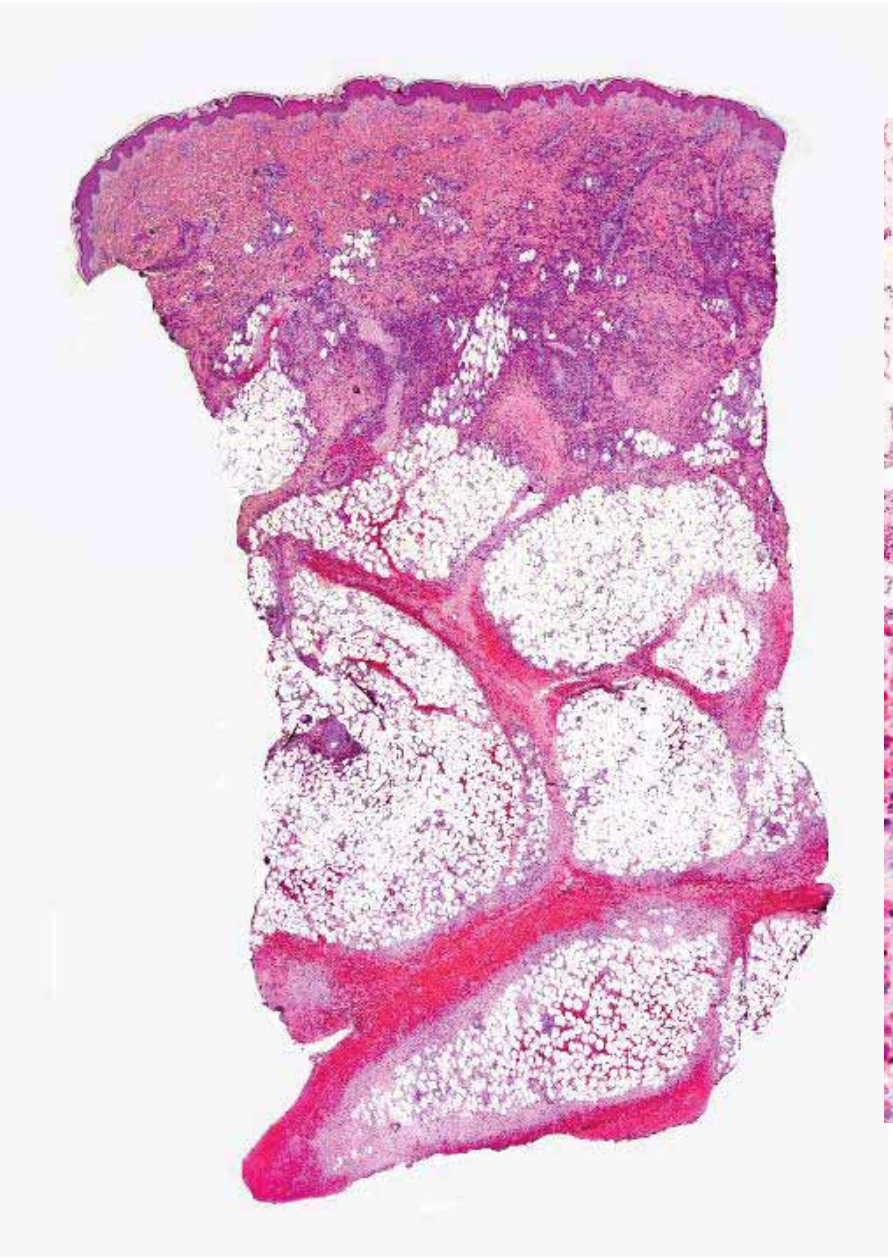
- Pruritic erythematous macules, papules, plaques or nodules.
- Urticaria and angioedema.
- Erythema annulare centrifugum-like lesions.
- Livedo reticularis, retiform purpura and superficial thrombophlebitis (almost exclusively in primary HES).

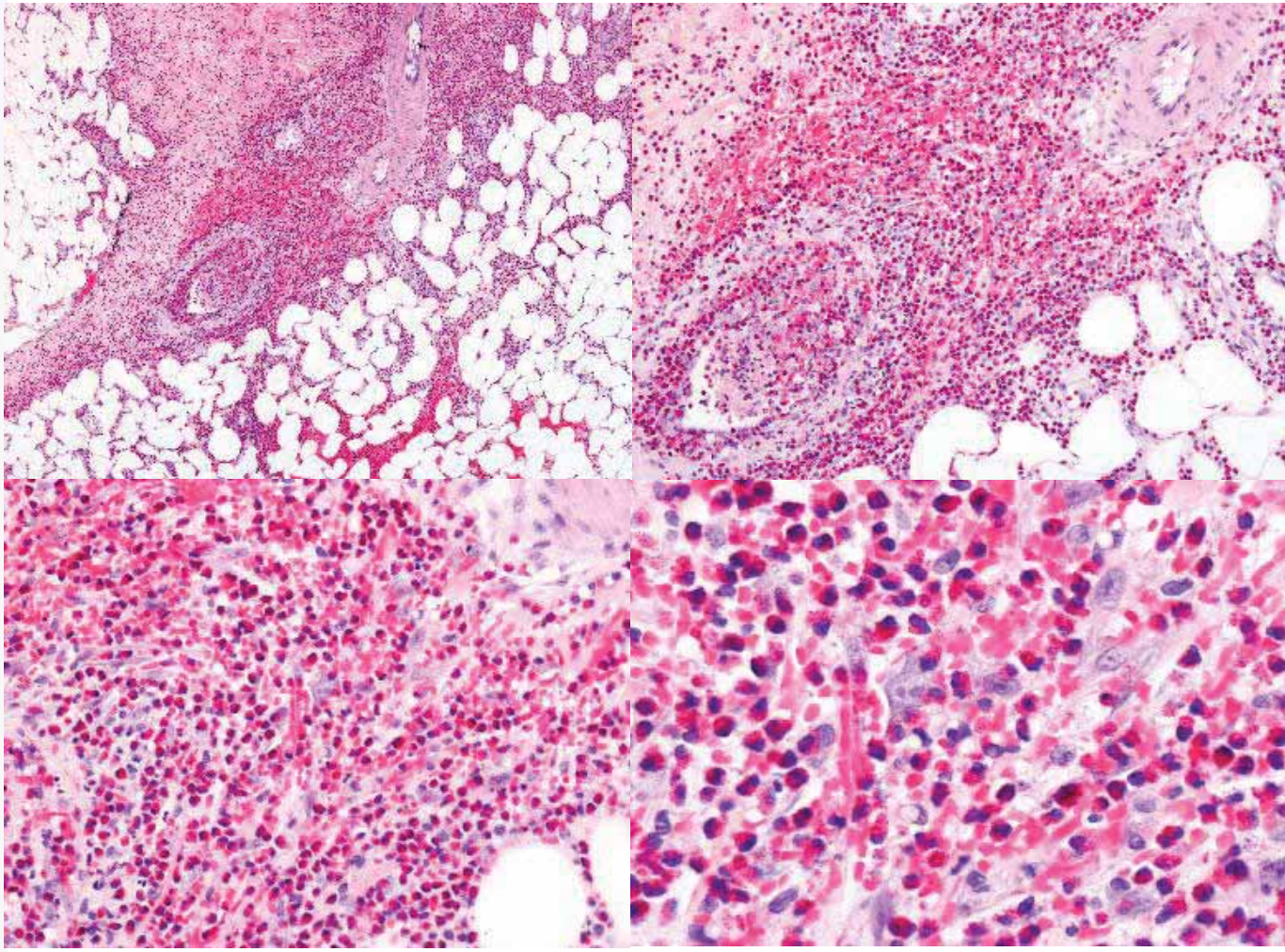


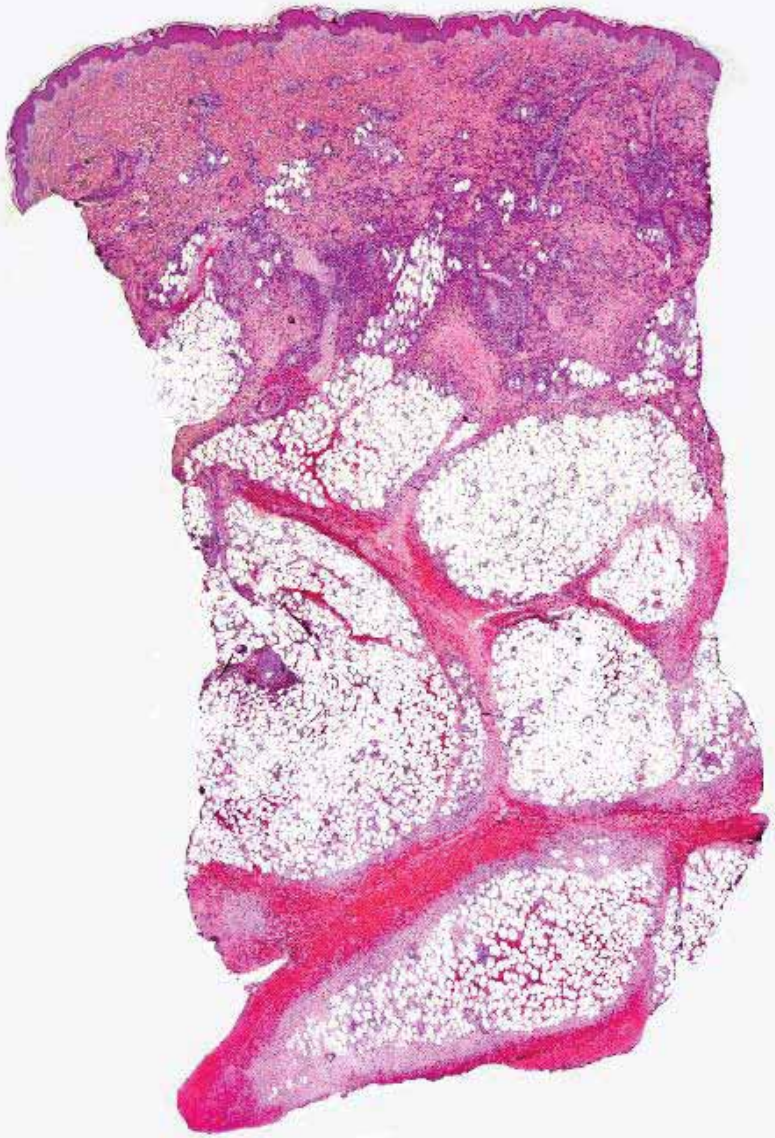
51-y-old Chinese male with history of asthma, blood hypereosinophilia, hypertrophic myocardiopathy, chronic urticaria, dermographism and indurated erythematous plaques on the posterior legs.

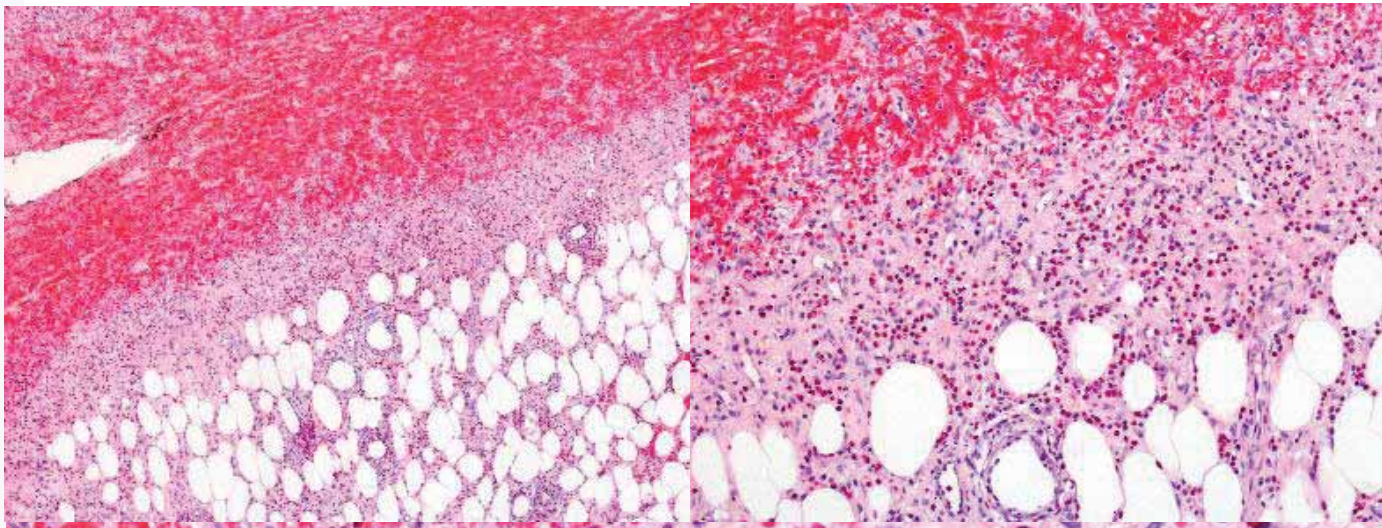


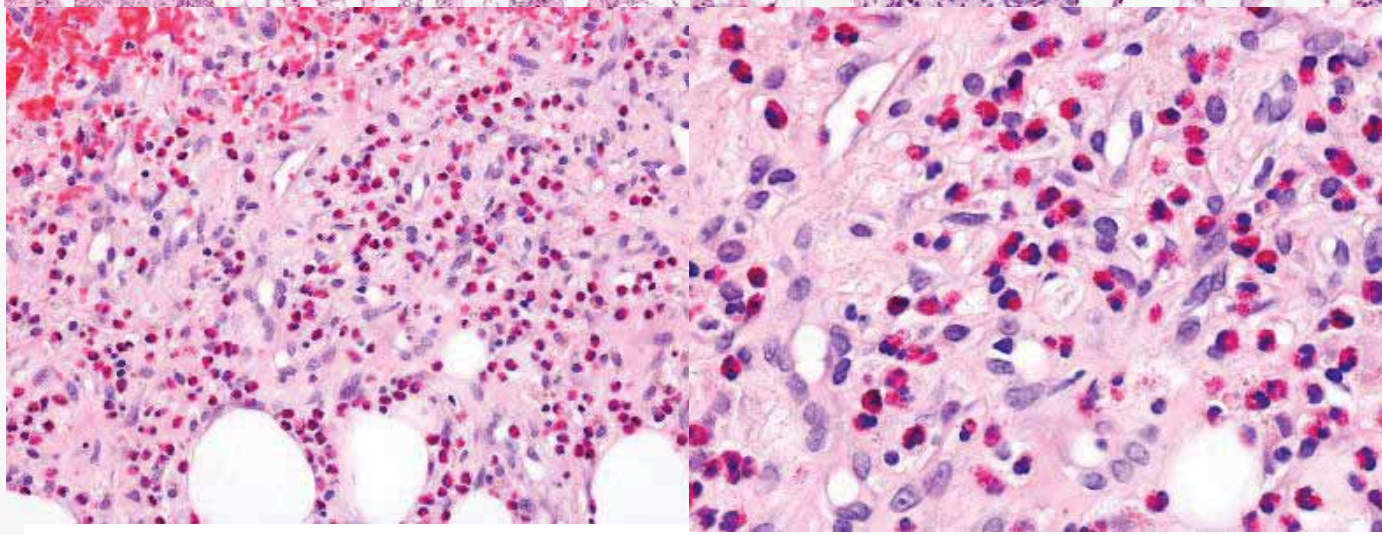


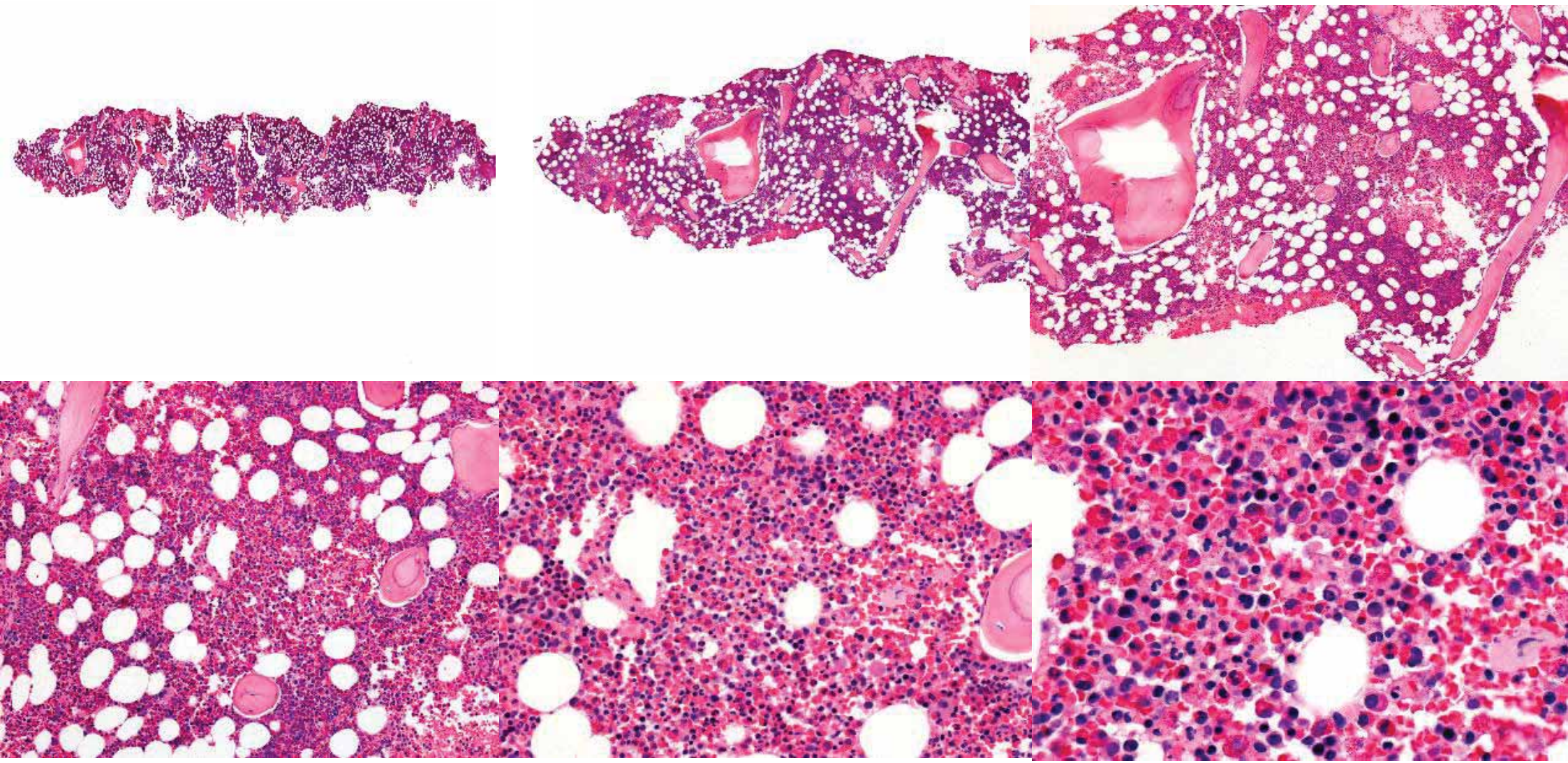












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Hospital Universitario Fundación Jiménez Díaz
Grupo quirónsalud

Nº Laboratorio: 41146401 **Fecha registro:** 23/02/2023 11:09 **Fecha edición:** 29/03/2023 12:08

Datos del paciente

Centro: Hospital Universitario Fundación Jiménez Díaz
Servicio: HEMATOLOGIA CLINICA - P
Doctor: ARRIERO GARCIA , ALVARO VALERIANO
Cobertura: .SERMAS resto zonas L.E.
Nº Cobertura: GNXX187103163
Información Adicional

Nombre: [redacted]
Nº Historia: 1558302 **Nº Identificación:** X6810666K
Sexo: VARON
Fecha de nacimiento (edad): 18/05/1971 (51 años)
Telf: 665812339

Inmunofenotipo por citometría de flujo

Prueba	Resultado	Unidades	Valores de Normalidad

Inmunofenotipo en médula ósea
Se distinguen las siguientes poblaciones:

- Serie roja: 12.07%

- Serie granulocítica: 54.41%

- Monocitos: 8.03%

- Eosinófilos: 24.81%

- Linfoide: 5.66%

* CD45++ CD3-+ CD5+ CD2+ CD7+: 3.84%

CD4+ : 1.54%

CD8+ : 1.85%

* CD45++ CD3- CD56+ CD2+ CD7- CD5 : 1.42%

* CD3- CD5- CD2- CD7- CD56- CD45 + : 0.4%

COMENTARIO

Muestra donde destaca un aumento en la proporción de eosinófilos maduros, junto con una proporción escasa de linfocitos. Dentro de ellos hay linfocitos T maduros que no expresan datos antigénicos anómalos con los marcadores estudiados (cociente TCD4+ /TCD8+: 0.83). También se observan células B maduras y escasas células NK.

CONCLUSIÓN: Hallazgos no sugestivos de infiltración por su LMH-T. A correlacionar con el resto de estudios.

Fdo: Dra. R. Mata

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Grupo quirónsalud

Nº Laboratorio: 41146401 **Nº de identificación:** X6810666K **Nombre:** [redacted]

FISH (fluorescencia por hibridación in situ) dual - color

Prueba	Resultado	Unidades	Valores de Normalidad

Reordenamiento FISH sangre: 1 sonda dual color

FISH EOSINOFILIA

Alteración	Resultado	% células
PDGFRA::FIP1L1	NEGATIVO	100%
PDGFRB	NEGATIVO	100%
FGFR1	NEGATIVO	100%
JAK2	NEGATIVO	100%

PROCEDIMIENTO

Se ha realizado un estudio de citogenética molecular mediante hibridación in situ con fluorescencia (FISH) sobre núcleos interfásicos. Se han analizado 200 núcleos interfásicos. Sondas utilizadas:
XL 4q12 DC Translocation/Deletion Probe (Metasystems, Cat#D-5123-100-OG)
Vysis PDGFRB Break Apart FISH Probe Kit (Abbott Molecular, Cat#06N24-010)
XL FGFR1 Break Apart FISH Probe (Metasystems, Cat#D-5041-100-OG)
XL JAK2 Break Apart FISH Probe (Metasystems, Cat#D-5098-100-OG)

FÓRMULA ISCN2020
nuc ish(PDGFRA,PDGFRB,FGFR1,JAK2)x2

Fdo.

Dra. M.Atance

Código de verificación

Madrid 29 de marzo de 2023 12:08

Responsable Laboratorio: **Ignacio Gadea Girones**

Fecha de toma de la muestra: 23 febrero 2023 11:09

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EOSINOPHILIC DERMATOSES

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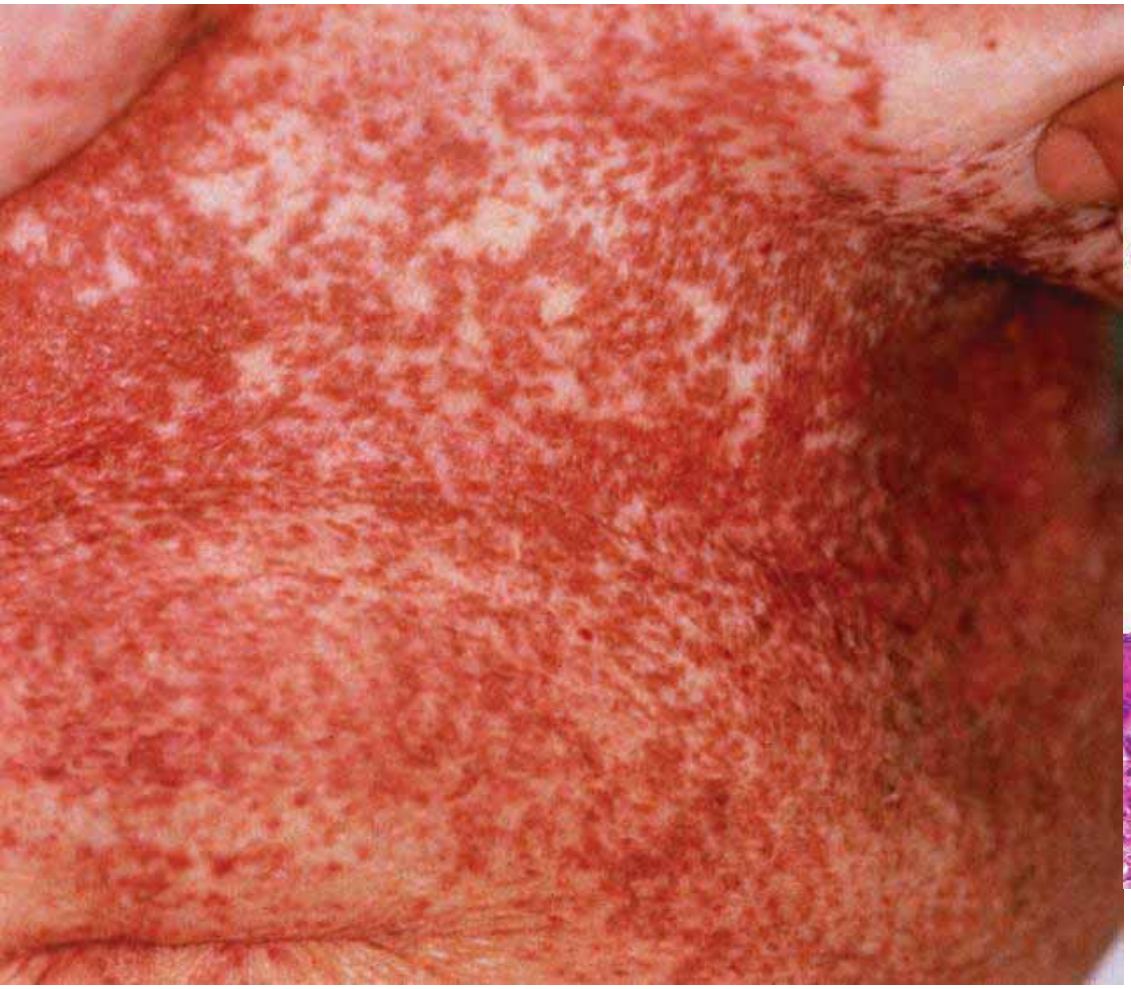

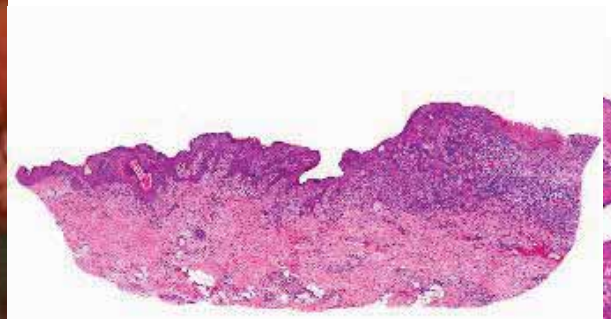

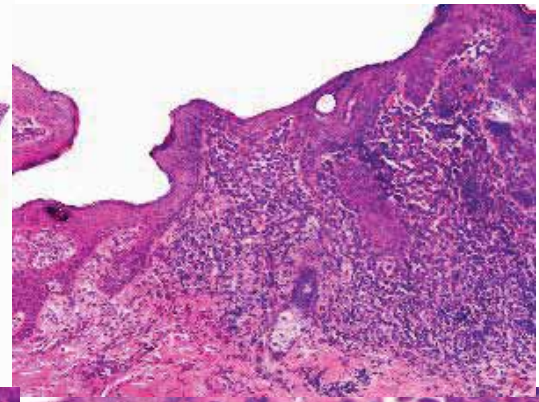

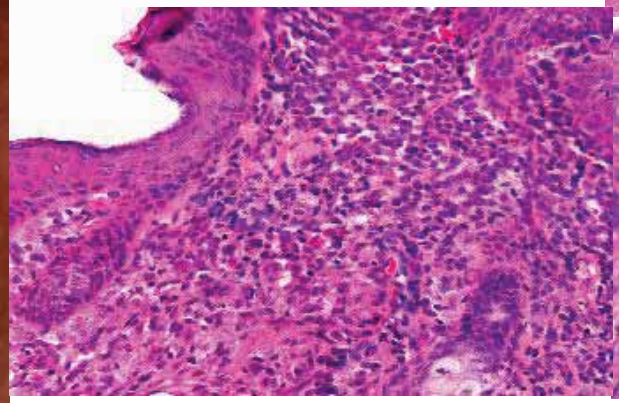

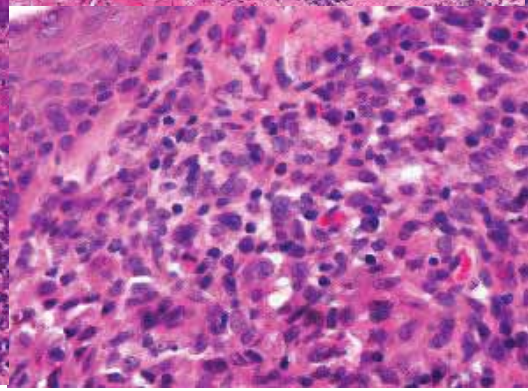

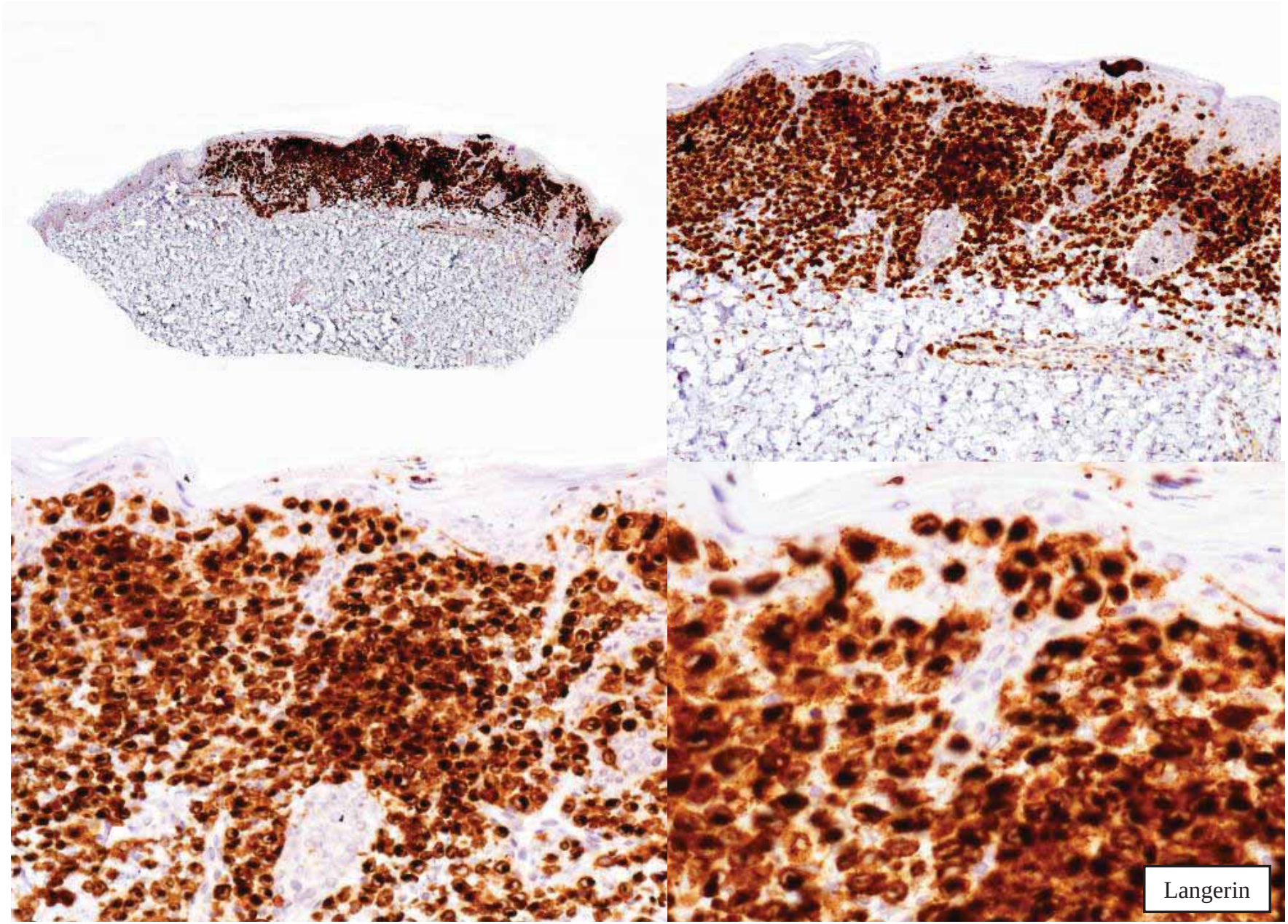
Langerin

Differential In Situ Cytokine Profiles of Langerhans-Like Cells and T Cells in Langerhans Cell Histiocytosis: Abundant Expression of Cytokines Relevant to Disease and Treatment

By R. Maarten Egeler, Blaise E. Favara, Marjan van Meurs, Jon D. Laman, and Eric Claassen

The pathogenesis of Langerhans cell histiocytosis (LCH) remains poorly understood. To further elucidate LCH pathogenesis, we analyzed the expression of 10 cytokines relevant to cellular recruitment and activation at the protein level in 14 patients and identified the lesional cells responsible for cytokine production in situ by immunohistochemistry. The cytokines investigated included the hematopoietic growth factors interleukin-3 (IL-3), IL-7, and granulocyte-macrophage colony-stimulating factor (GM-CSF); the lymphocyte regulatory cytokines IL-2, IL-4, and IL-10; the inflammatory regulators IL-1α and tumor necrosis factor-α (TNF-α); and the effector cell-activating cytokines IL-5 and interferon-γ (IFN-γ). In all specimens, CD1a+ histiocytes (LCH cells) and CD3+ T cells produced large amounts of cytokines, creating a true cytokine storm. IL-2, IL-4, IL-5, and TNF-α were produced exclusively by T cells, whereas only IL-1α was produced by LCH cells. Equal numbers of LCH cells, T cells, and macrophages produced GM-CSF and IFN-γ. Equal numbers of LCH cells and macrophages produced IL-10, whereas IL-3 was produced by T cells and macrophages. IL-7 was only produced by macrophages. Eosinophils, present in some specimens, were partially responsible for the production of IL-5, IFN-γ, GM-CSF, IL-10, IL-3, and IL-7. Expression of all cytokines, abundant in most biopsies, was irrespective of age, gender, or site of biopsy. These findings emphasize the role of T cells in LCH. The juxtaposition of T cells and LCH cells suggests that both cells interact in a cytokine amplification cascade, resulting from stimulation of autocrine and paracrine stimulatory loops. This cascade can be linked directly to the development of LCH through recruitment, maturation, and proliferation of LCH cells. The cytokines studied are known to be involved in the development of other characteristic features of LCH, such as fibrosis, necrosis, and osteolysis.

LANGERHANS CELL histiocytosis (LCH), a rare disorder, mainly of children, is of unknown pathogenesis with variable course.[1] The broad clinical spectrum of disease ranges from a single lytic lesion of bone that is usually cured by simple curettage to a disseminated leukemia-like illness with significant mortality. Intermediate forms of disease are chronic, often with multiorgan involvement and diabetes insipidus.[2] Lesions of LCH are polymorphous, featuring a monoclonal population of $CD1a^+$ histiocytes with a phenotype akin to that of cells of the antigen-presenting Langerhans cell family. T cells, macrophages, and eosinophils are variably present. The key histiocyte of LCH and its normal counterpart, the Langerhans cell, express CD1a and S-100 and contain Birbeck subcellular organelles.[2] In contrast to normal Langerhans cells, the principal histiocytes of LCH (LCH cells) are actively proliferating, have a round rather than dendritic shape, and express several contrasting antigenic markers.[1]

The morphology of LCH lesion and the clinical signs and symptoms of disease suggest that cytokines may be important in the pathogenesis of the disorder. Using immunohistochemistry and reverse transcription-polymerase chain reaction (RT-PCR), upregulation of the following cytokines in LCH lesions has previously been shown: interleukin-1 (IL-1), IL-3, IL-4, IL-8, granulocyte macrophage colony stimulating factor (GM-CSF), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), and leukemia inhibitory factor (LIF).[3-6] These studies did not identify the cellular source of these cytokines in the LCH lesion. We have previously developed methods to analyze cytokine expression at the protein level in situ so as to establish the identity of cells producing an array of cytokines for both human and mouse tissues.[7,8] Using validated antibody-based immunohistochemistry, intracellular cytokine present in cytokine producing cells can be reliably visualized, and double-staining techniques for CD markers allow unequivocal identification of the cell type producing the cytokine. We used these methods here to analyze the expression of an extended panel of cytokines relevant to LCH pathogenesis and to identify their cellular origin in 14 LCH lesions. We demonstrate that T cells and LCH cells are the major local sources of cytokines, which are involved in recruitment and survival of Langerhans cells, as well as in their maturation into effector cells contributing to LCH pathogenesis.

MATERIALS AND METHODS

A definitive diagnosis of LCH and the representative nature of 14 specimens from 14 cases were confirmed by BEP. Eleven of the

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These studies were initiated through the Nikolas Symposium (organizers Paul and Elizabeth Kountzounis). The Histiocytosis Association of America and the Histiocytosis Stichting in The Netherlands provided additional financial support.

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Recruitment and differentiation of cells. Previously, lesions of LCH have been shown to contain mRNA transcripts for IL-1, IL-3, IL-4, IL-8, GM-CSF, TNF-α, TGF-β, and LIF. No transcripts for IL-2, IL-5, IL-6, or IFN-γ were found.[6] Using immunohistochemistry, De Graaf et al[5] showed that cells in LCH lesions and those from normal and allergic skin expressed IL-1α, IL-1β, GM-CSF, TGF-α, TGF-β, TNF-α, and IFN-γ, whereas LCH cells alone did not express basic fibroblast growth factor. The cytokine IL-2 was not studied.[5] Our data complete these findings in showing that crucial immunologic active cytokines, such as IL-2, IL-5, and IFN-γ, are, indeed, produced by lesional T cells and that LCH cells produce IFN-γ, but they do not produce IL-2 and IL-5. Because under physiological conditions IL-3 can stimulate the generation and differentiation of progenitor cells of every lineage derived from the pluripotential hematopoietic stem cells, IL-3 might contribute to the differentiation of LCH cell progenitors.

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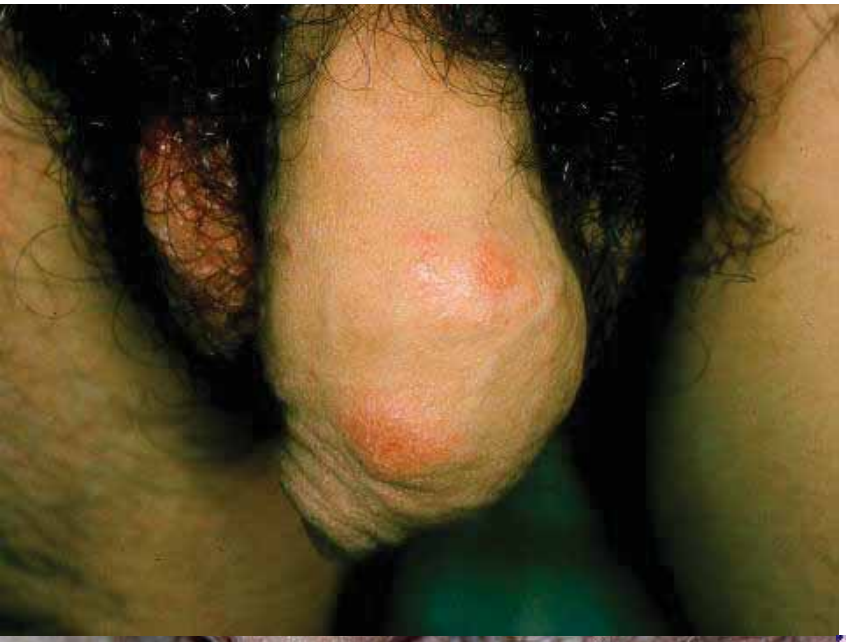

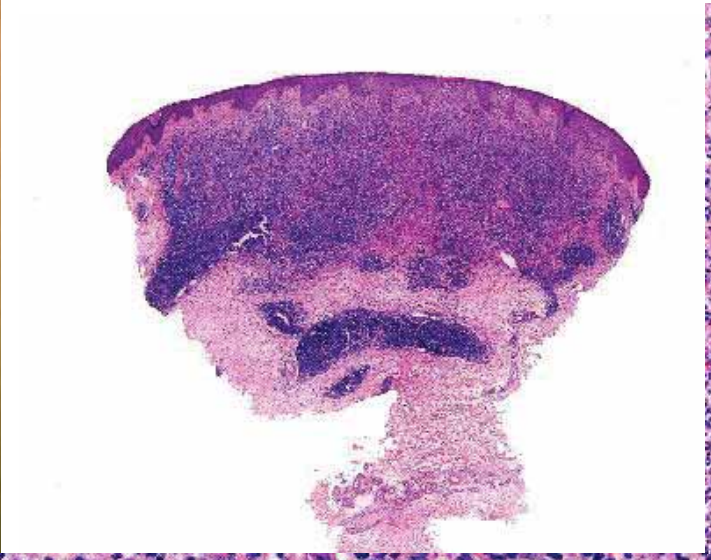

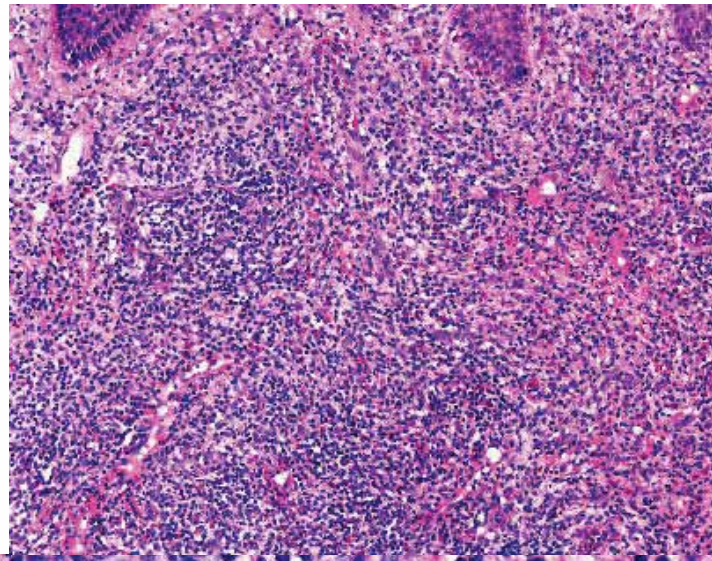

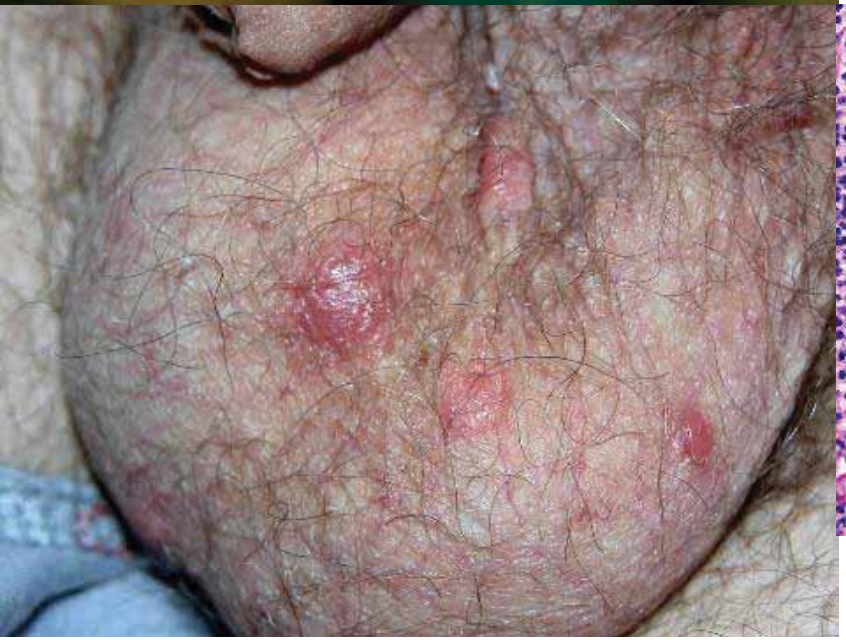

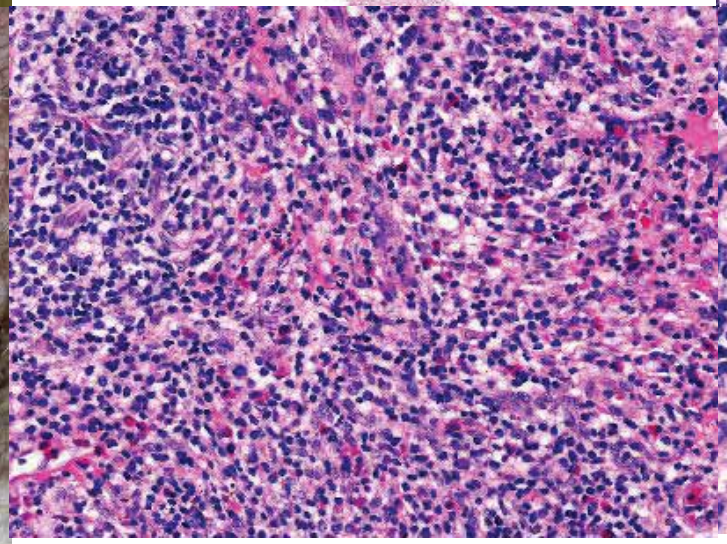

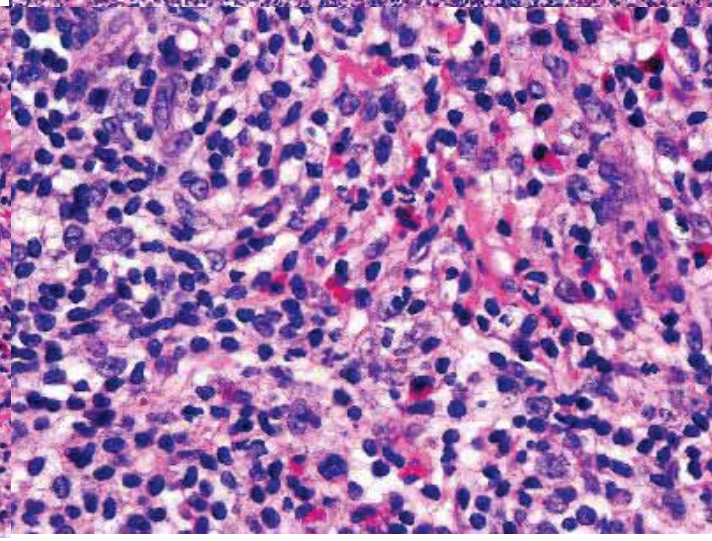

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CD30 antigen expression in cutaneous inflammatory infiltrates of scabies: a dynamic immunophenotypic pattern that should be distinguished from lymphomatoid papulosis

Fernando Gallardo, Carlos Barranco[1], Agustí Toll and Ramon M. Pujol

Departments of Dermatology and [1]Pathology, Hospital del Mar, IMAS, Barcelona, Spain

Background: Expression of CD30 antigen is a distinct marker of lymphocyte activation that was originally described in the Reed–Sternberg cells of Hodgkin's disease. The observation of CD30$^+$ cells has been considered a diagnostic feature of cutaneous CD30 lymphoid proliferations. However, CD30 expression has also been reported in some cutaneous benign inflammatory infiltrates.
Methods: Eleven skin biopsies from patients with scabies were double-blindly and retrospectively analysed. A panel of histopathological parameters and immunophenotypic expression of CD4, CD8, CD30 and S-100 antigens was studied. CD30 and S-100 antigens expression were related to clinical features.
Results: Large CD30$^+$ cells were demonstrated in eight (8/ 11) biopsies, corresponding to patients with long-standing lesions (3 months or longer). However, no expression of the CD30 antigen was observed in all biopsy specimens (3/ 11) corresponding to early lesions (2 months or less). The presence of S-100 positive cells in the papillary dermis was an almost constant feature.
Conclusions: CD30$^+$ large cells seem to be a common feature in long-standing infiltrates of scabies. CD30 expression in scattered cells of a cutaneous lymphoid infiltrate cannot be assessed as a strong diagnostic argument of neoplastic cutaneous CD30$^+$ lymphoid proliferation (lymphomatoid papulosis/ cutaneous CD30$^-$ lymphoma). Therefore, the possibility that large atypical CD30$^+$ cells may be also present in several benign inflammatory diseases should be always considered.

Gallardo F, Barranco C, Toll A, Pujol RM. CD30 antigen expression in cutaneous inflammatory infiltrates of scabies: a dynamic immunophenotypic pattern that should be distinguished from lymphomatoid papulosis.
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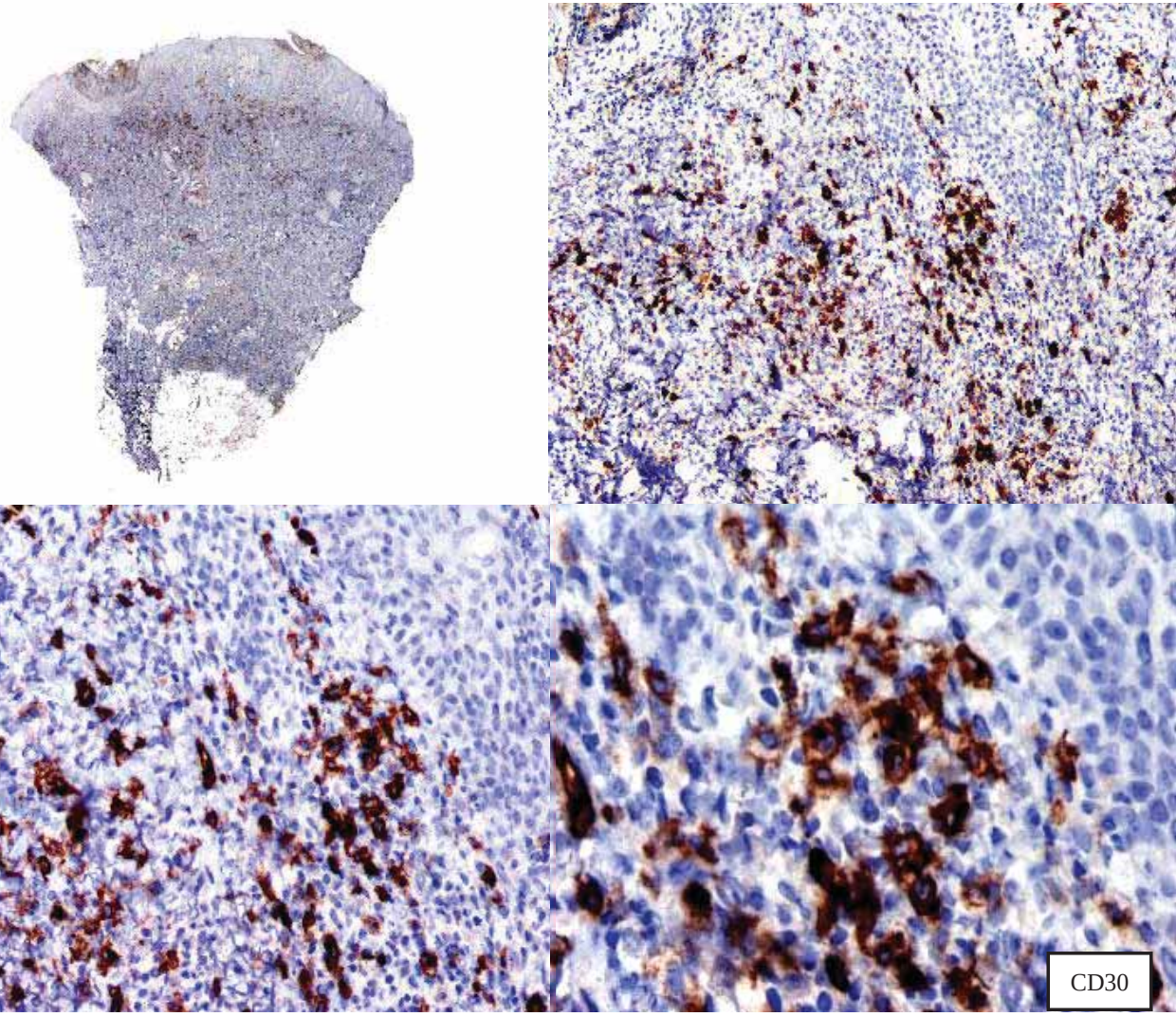
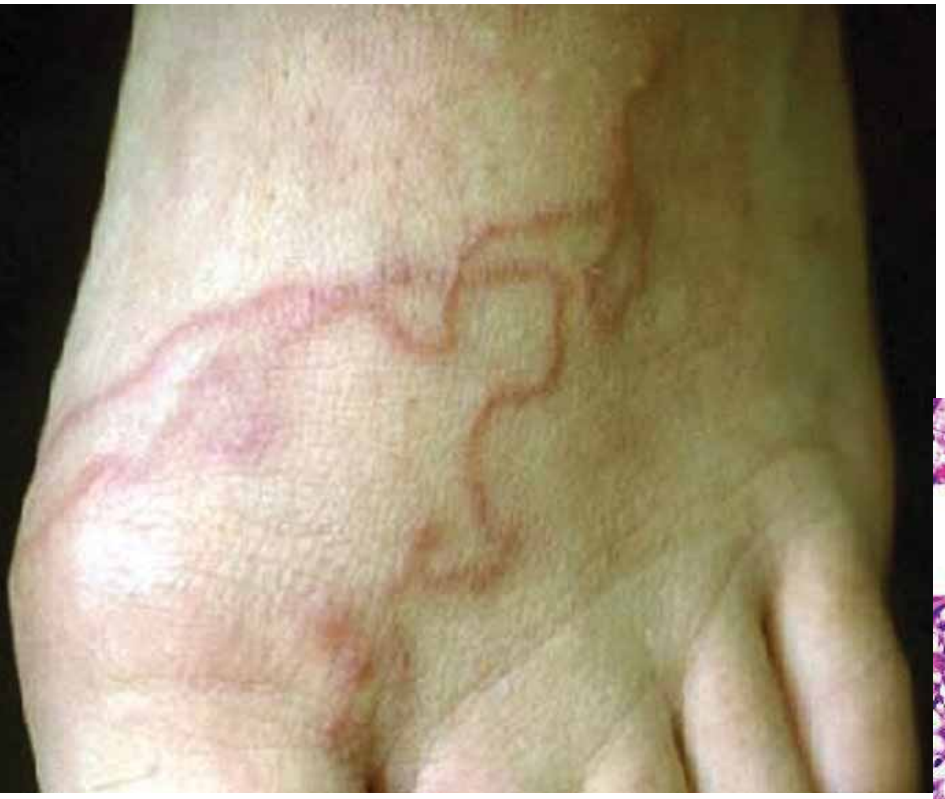
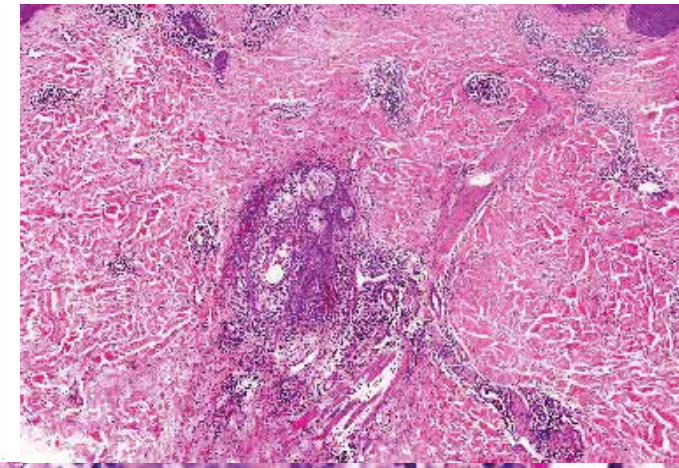
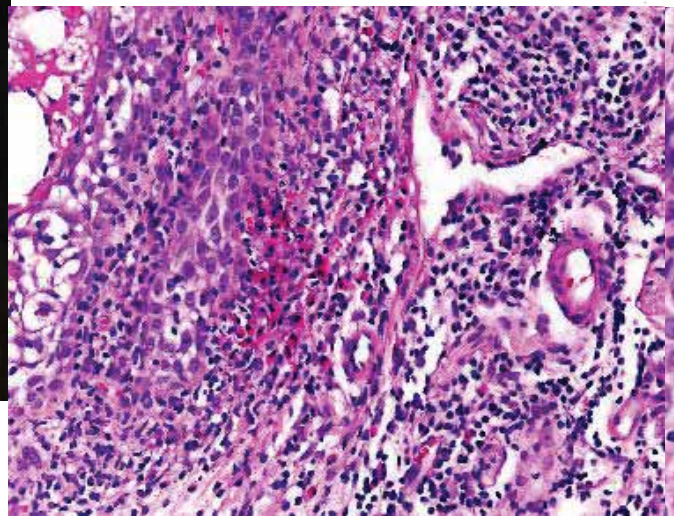
CD30 antigen is a member of the to the tumor necrosis factor (TNF)/ nerve growth factor (NGF) receptor family and represents a marker of lymphocyte activation.[1] Its expression was initially described in the Reed–Sternberg cells of Hodgkin's disease. CD30 antigen expression in neoplastic nodal lymphoid infiltrates makes possible to distinguish a type of lymphoma (anaplastic lymphoma CD30$^-$) with special features and better clinical behaviour.[2]

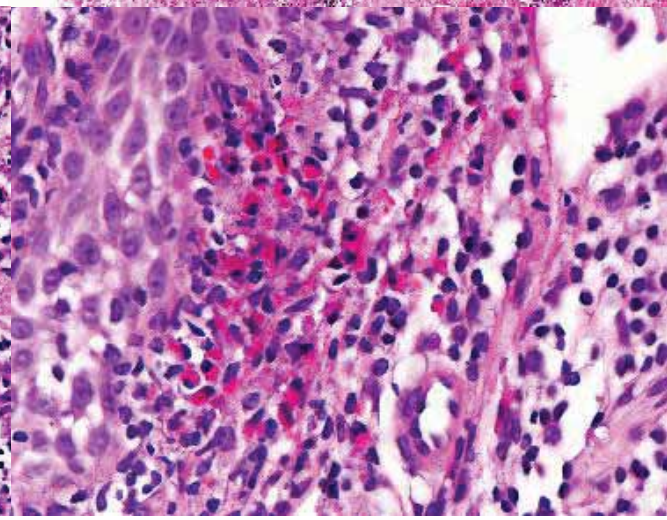
CD30 antigen expression in skin infiltrates in large

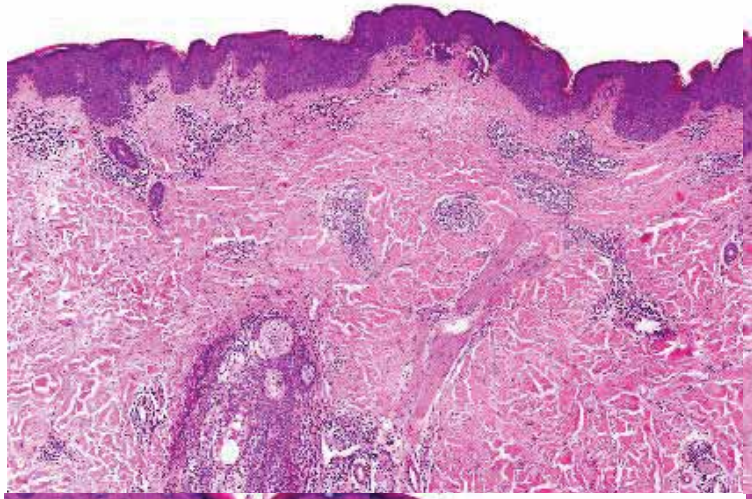
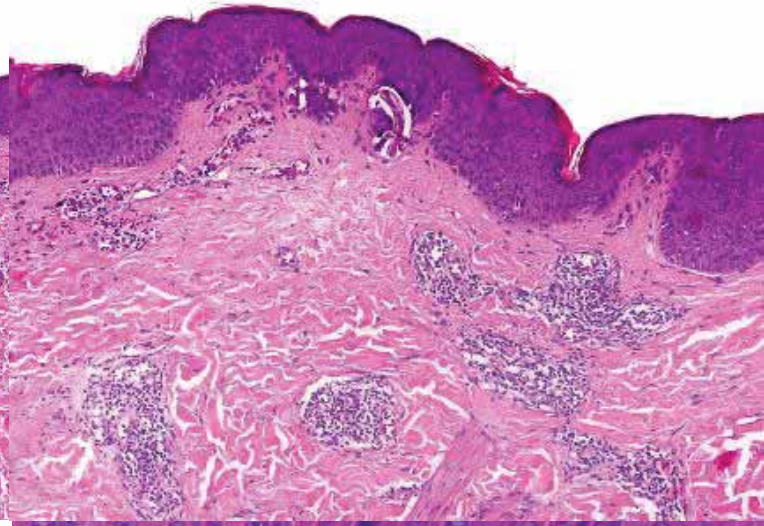
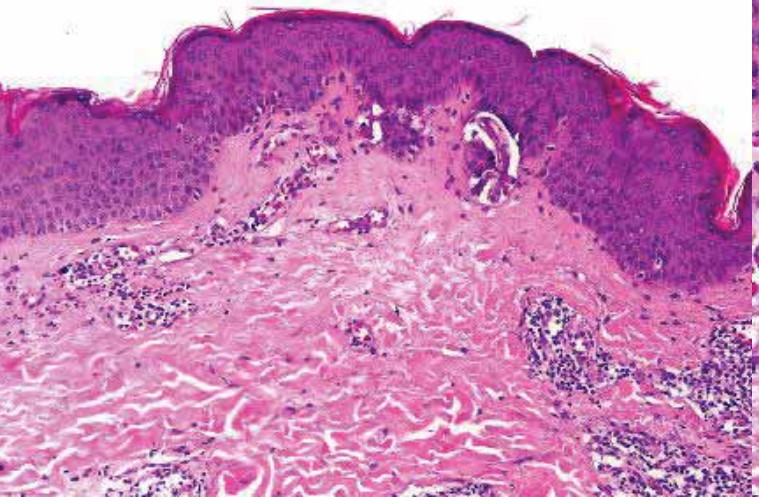
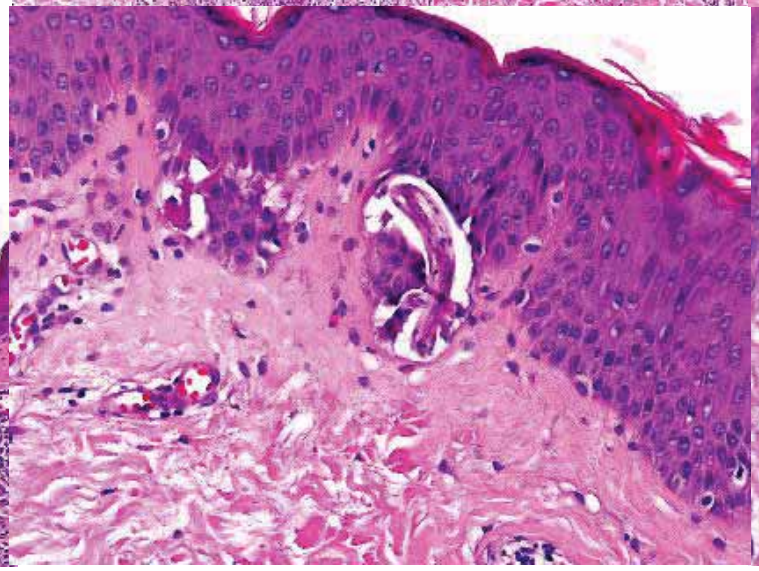
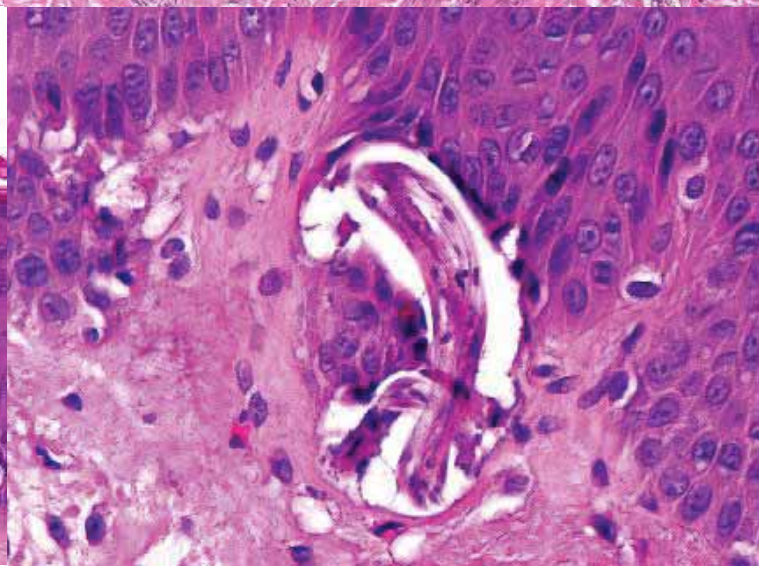










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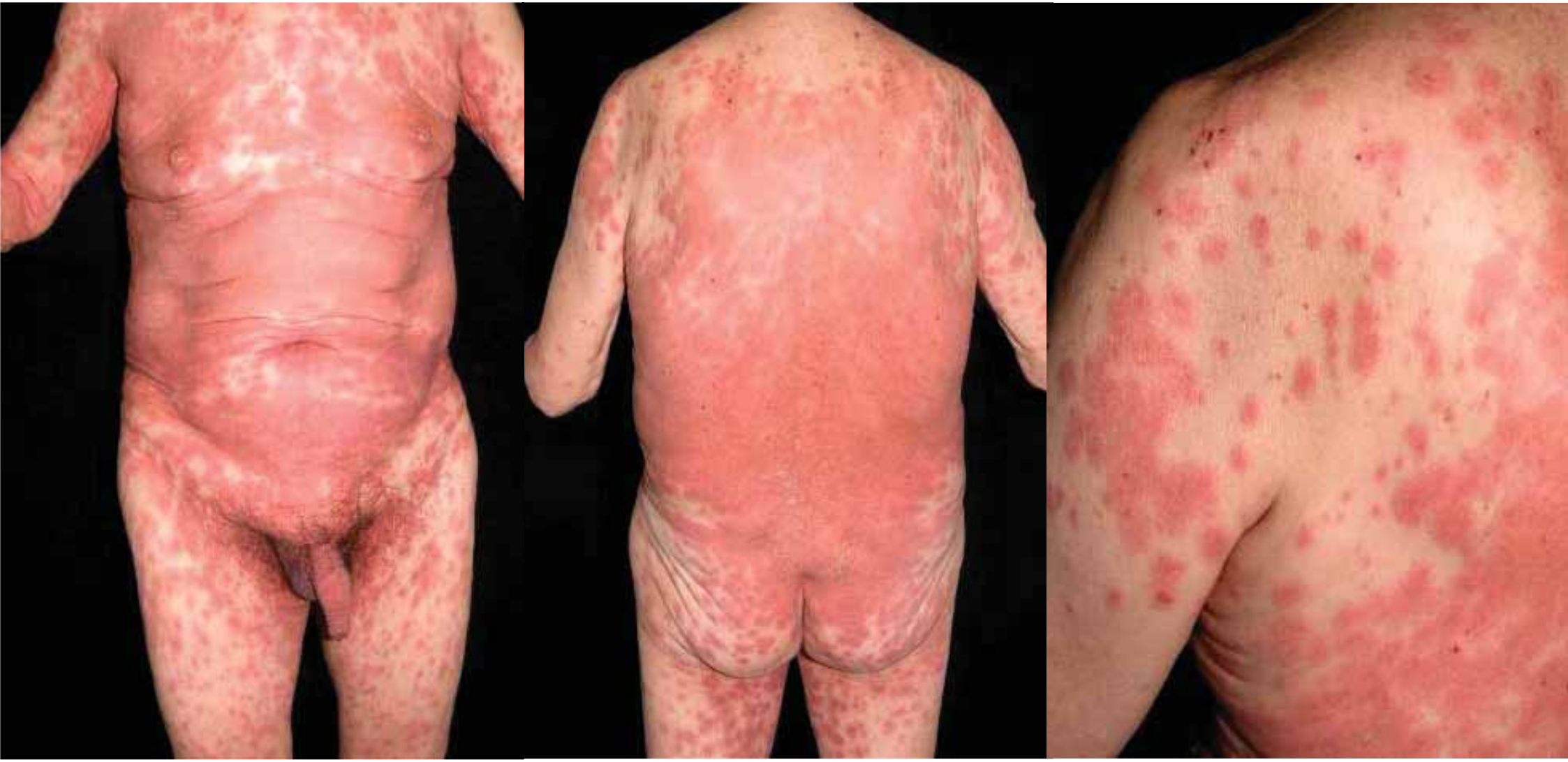
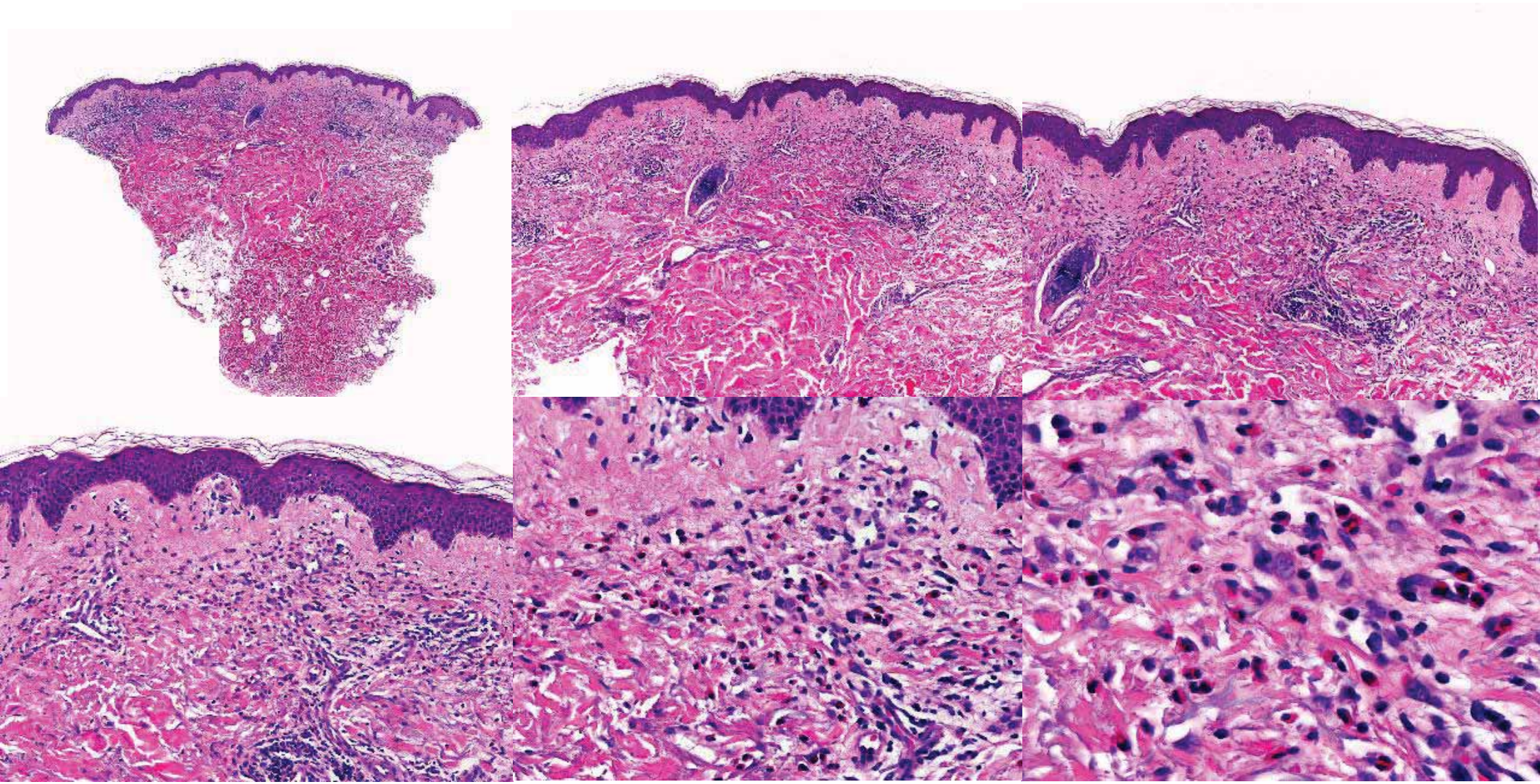
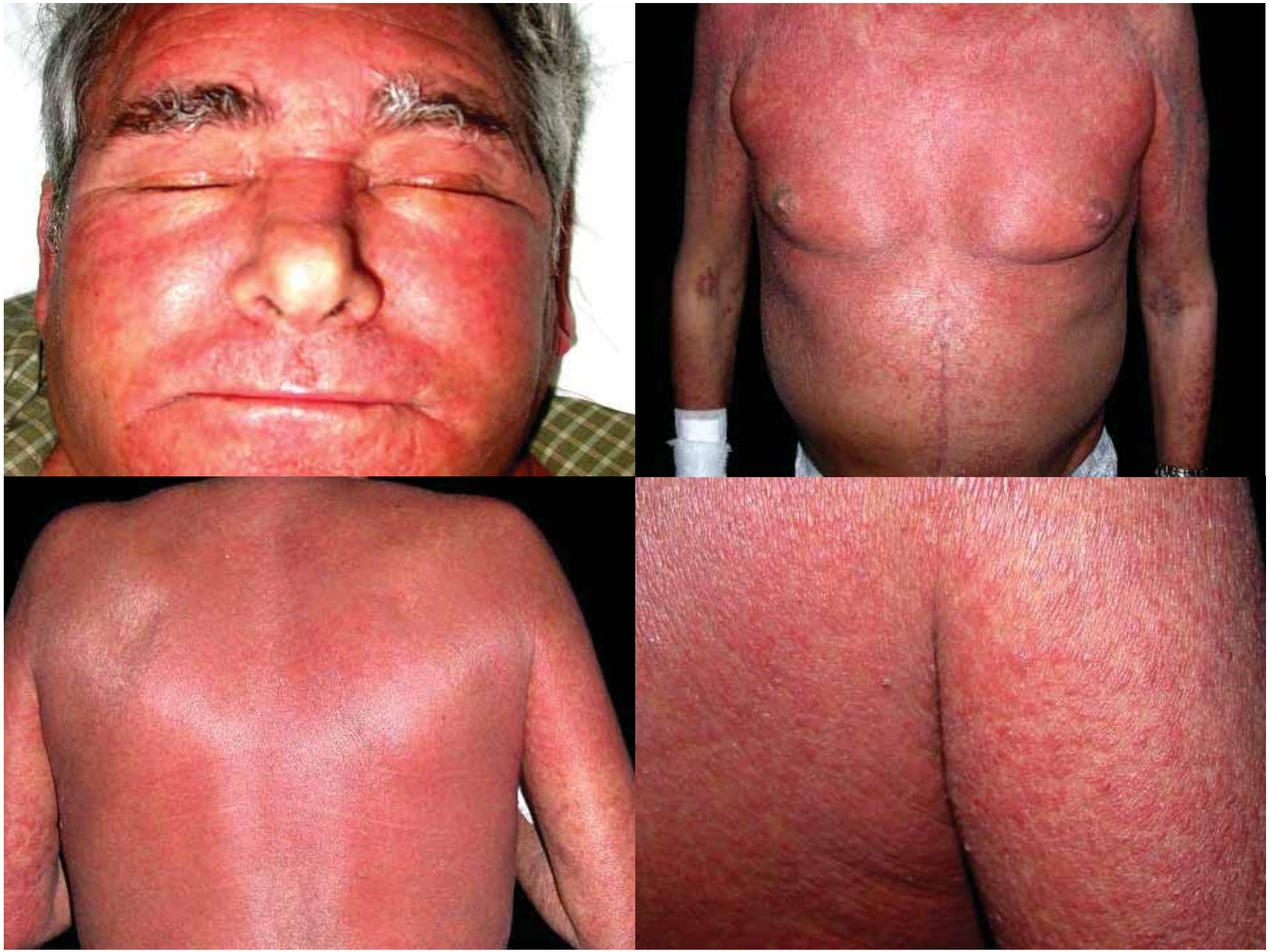






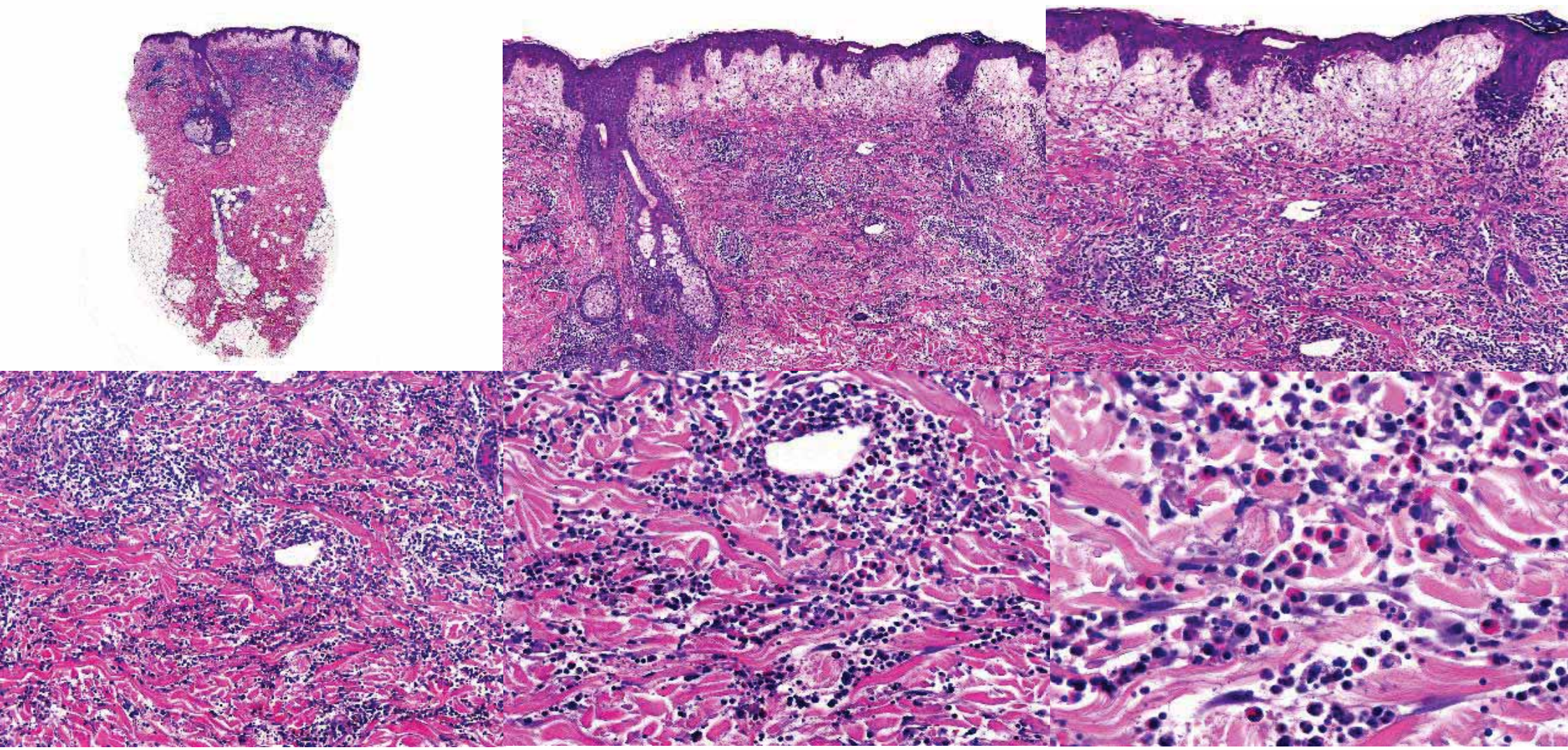
DRESS DIAGNOSTIC CRITERIA (regisCAR)

Criteria	No	Yes	Unknown
Fever >38.5°C	−1	0	−1
Lymphadenopathy	0	1	0
Skin rash >50% body surface	0	1	
Edema, infiltration, scaling	−1	1	
Resolution in >15 days	−1	0	−1
Atypical lymphocytes	0	1	0
Blood eosinophilia	0	1	
10–19.9% or 700–1499 Gpt/l		2	
>20% or >1500 Gpt/l			
Evaluation of other potential causes	0	1	0
(antinuclear antibodies, blood culture, hepatitis A, B, C serology, chlamydia/mycoplasma)			

*Heart, liver, kidney, muscle, pancreas or other

Scores 1–3: diagnosis uncertain; score 4 or higher: diagnosis certain

Paulmann M and Mockenhaupt M. Severe drug hypersensitivity reactions: clinical pattern, diagnosis, etiology and therapeutic options. Current Pharmaceutical Design 2016;22::6852-6861



DRESS. Histopathologic features

- Several histopathologic patterns: spongiotic, interface dermatitis, AGEP-like, erythema multiforme-like and interstitial granulomatous dermatitis have been described.
- Eosinophils are almost always present in the infiltrate.
- In some instances: dense band-like superficial dermal lymphocytic infiltrate and dermal edema.

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ORIGINAL ARTICLE

Drug reaction with eosinophilia and systemic symptoms (DRESS): clinicopathological study of 45 cases

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Abstract

Background Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare and severe adverse drug reaction. Large detailed studies of histopathological features of DRESS are scarce and suggest an association between keratinocyte damage and the severity of visceral involvement.

Objectives To describe the dermatopathological features in a large series of DRESS and their possible association with clinical features and the severity of the disease.

Methods A retrospective analysis of the clinicobiological and dermatopathological features in a monocentric cohort of patients with DRESS.

Results From January 2000 to January 2013, 45 patients were validated as probable or definite cases of DRESS. The median age was 64 years (range 3–87). The most frequent clinical and biological features included: fever >38.5°C (85%), facial oedema (72%), enlarged lymph nodes (51%), visceral involvement (75%), blood eosinophilia (97%) and atypical lymphocytes (82%). Severe DRESS occurred in 24% and a fatal outcome in 9% of patients. Histopathological analysis showed that no specific histopathological pattern was characteristic for DRESS. However, several changes in different cutaneous compartments were observed in 2 of 3 of cases. Spongiosis (55%) and keratinocyte damage (53%) were the most common epidermal changes. Spongiosis was associated with non-severe DRESS ($P = 0.041$) whereas confluent keratinocyte necrosis correlated with severe DRESS ($P = 0.011$). Vascular changes were frequent (88%). A moderate dermal perivascular lymphocytic infiltrate was invariably present, containing eosinophils, neutrophils and/or atypical lymphocytes in 57% of cases.

Conclusions Epidermal changes are indicative for the severity of DRESS.

Received: 27 February 2015; Accepted: 22 May 2015

Conflicts of interest

None

Funding sources

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Introduction

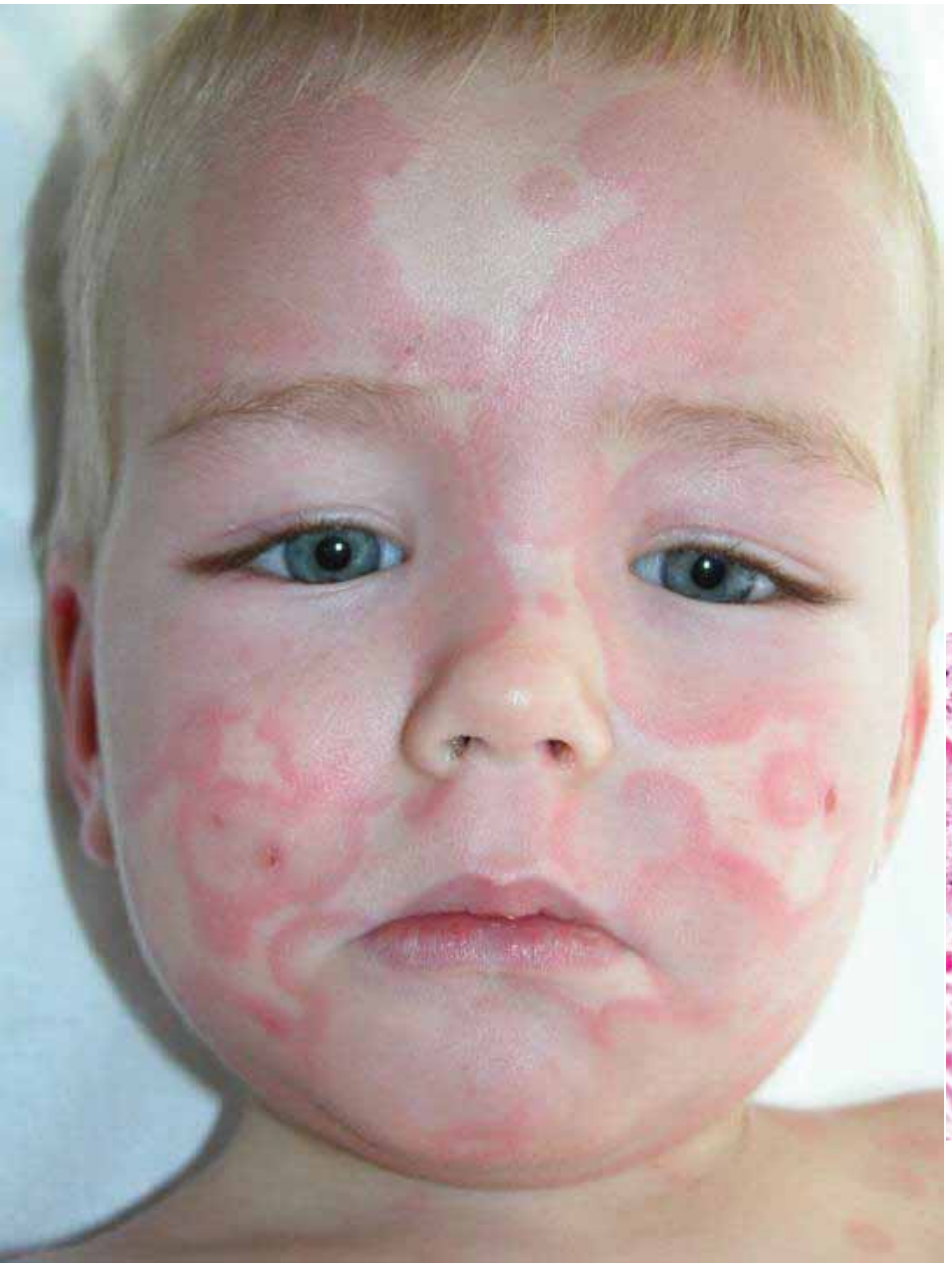
Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe adverse drug reaction.[1,2] The skin is the most frequently involved organ in DRESS and is easily accessible for histopathological examination. However, large detailed studies of histopathological features of DRESS are sparse.[3–5] The most frequently reported changes include spongiotic dermatitis, keratinocyte damage, lymphocytic exocytosis, dermal oedema,

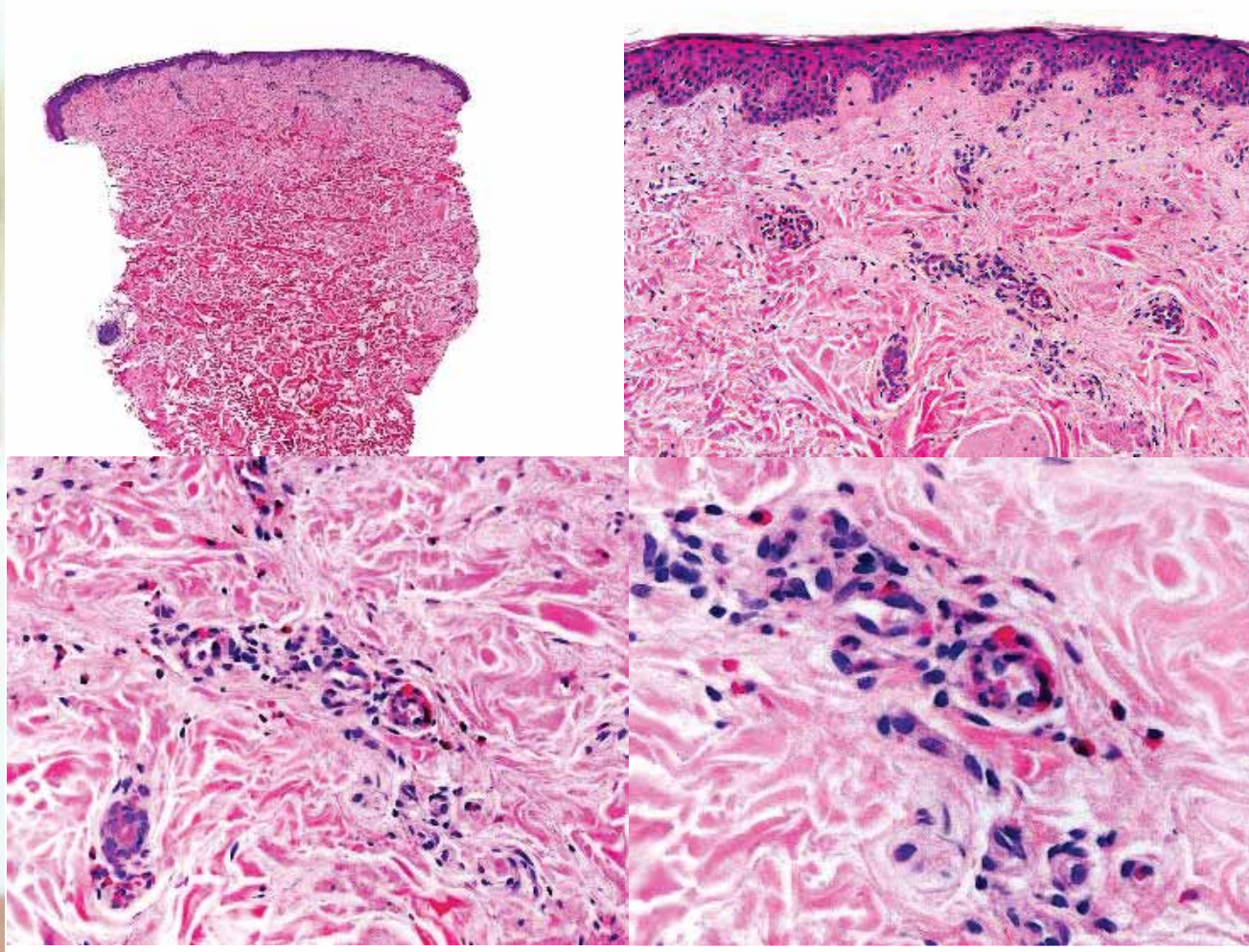
*Contributed equally to the study.

- Spongiosis (55%) and keratinocyte damage (53%).
- Confluent keratinocyte necrosis was associated with severe DRESS.
- A moderate dermal perivascular lymphocytic infiltrate was invariably present, containing eosinophils, neutrophils and/or atypical lymphocytes in 57% of cases.

EOSINOPHILIC DERMATOSES

Eosinophil location	Clinical pattern	Disorder
Epidermis	Eczematous	Atopic dermatitis Contact dermatitis Cutaneous T cell lymphoma Hypereosinophilic syndrome with cutaneous manifestations Langerhans cell histiocytosis Scabies and larva migrans
Dermo-epidermal junction	Macular and papular	Drug eruption DRESS
Papillary dermis	Urticarial	Urticaria Eosinophilic cellulitis (Wells syndrome) Episodic angioedema with eosinophilia (Gleich syndrome) Polymorphic eruption of pregnancy
Subepidermal/papillary dermis and hair follicles	Blisters and pustules	Bullous pemphigoid Pemphigus Incontinentia pigmenti Eosinophilic pustular folliculitis Erythema toxicum neonatorum
Papillary and reticular dermis	Papular and nodular	Insect bite Prurigo nodularis Eosinophilic annular erythema Eosinophilic cellulitis (Wells syndrome) Angiolymphoid hyperplasia with eosinophilia and Kimura disease Eosinophilic dermatosis associated with hematologic malignancy Primary cutaneous CD30+ lymphoproliferative disorders
Subcutis	Panniculitic	Erythema nodosum Parasitic panniculitis
Superficial vascular dermal plexus	Vasculitic	Eosinophilic vasculitis Granuloma faciale Eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease)
Fascia	Fibrosis and sclerosis	Localized scleroderma Systemic sclerosis Eosinophilic fasciitis





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RECURRENT GRANULOMATOUS DERMATITIS WITH EOSINOPHILIA

G. C. WELLS

Over the past ten years or so we have had under observation a small group of patients with an obscure, recurrent dermatosis which combines a striking clinical picture with a very remarkable histopathology. The late Dr. Henry Haber and I had planned to present a paper based on three of these cases at the 12th International Congress of Dermatology in 1962 under the title of 'Recurrent cutaneous swellings with necrobiosis and eosinophilia', but Dr. Haber's tragic death compelled us to withdraw this contribution. I am now able to return to these three cases and to add a fourth ; and, on reflection, I have dropped the reference in the title to necrobiosis. My further experience leads me to group these cases under the heading of 'Recurrent granulomatous dermatitis with eosinophilia', with the suggestion that this may have some relation to the allergic granulomatosis of Churg and Strauss (1951).

While I am only too well aware of the inadequacy of this contribution, I have hopes that it may appeal to Dr. Geoffrey Dowling in two respects. In the first place, three of the patients described below were seen by him, and he recognized that none of them fell within any diagnostic category with which he was familiar. Secondly, a major part of the interest lies in the extraordinary histopathology peculiar to this condition. Dr. Dowling came to dermatology after experience in general pathology and throughout his career he has maintained an eager interest in skin histopathology and has communicated this interest to his followers. His particular encouragement to Dr. Henry Haber when he was establishing histopathology at the Institute of Dermatology in London may be recalled by this paper.

The four patients recorded here illustrate a changing symptom complex with a phase of the disease characterised by episodes of acute 'eosinophilic cellulitis' followed by 'granulomatous dermatitis' with its distinctive histopathology.

CASE REPORTS

CASE I

History

This male clerk was first seen at St. Thomas' Hospital in 1958 when his age was 42, and when he had been getting periodic cutaneous swellings for about three years.

His past health had been good except for hip trouble at the age of 14. This was suspected of being tuberculous but it was not proven. Since early childhood he had been subject to transient itchy rashes on the limbs in the warmer weather, but he insists that the recent severe swellings have been quite different. There was no family history of similar cutaneous swellings.

His eruptions start with an area of redness and swelling with irritation. Over one or two days the oedematous swellings spread outward and might cover the whole extent of a limb (Fig. 1). The lesions are usually single, but may on occasion be multiple. The swellings show a distinct rosy or violaceous border. A brawny, bluish oedema persists for three or four weeks and slowly regresses, leaving the appearance of atrophy with slate grey pigmentation which slowly fades over a month or two.

FIG. 2

FIG. 3a

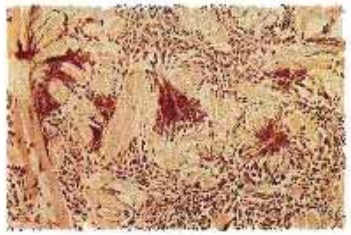


FIG. 3b

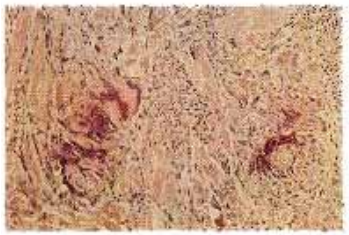


FIG. 4

FIG. 2.—Dermis evenly infiltrated with oedema, eosinophils and lymphocytes. Scattered flame figures.

FIG. 3a and b.—Flame figures. Eosinophil debris adhering to collagen.

FIG. 4.—Phagocytes and multinucleate cells separating connective tissue bundles.

FIG. 5.—Phagocytosis of disintegrating eosinophils. Eosinophil granules within giant cells.

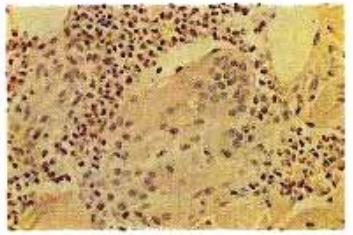


FIG. 5

Trans St Johns Hosp Dermatol Soc 1971;57:46-56.

British Journal of Dermatology (1979) **100**, 101.

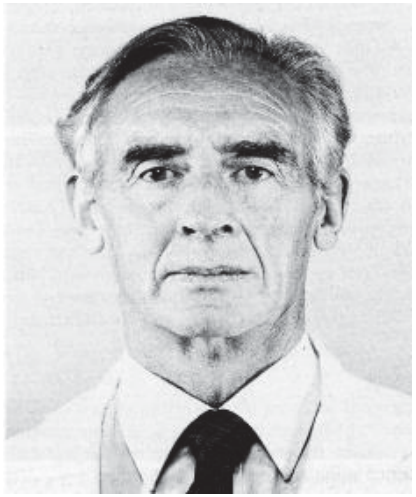
Eosinophilic cellulitis

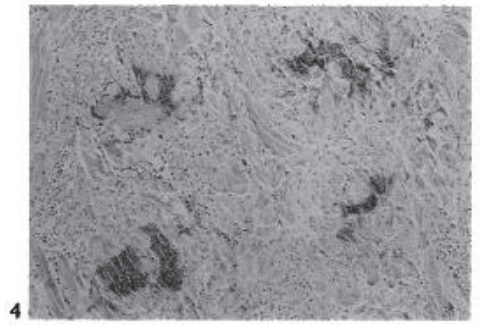
G.C.WELLS AND NEIL P.SMITH

St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
and St John's Hospital for Diseases of the Skin, Lisle Street, Leicester Square, London WC2H 7BJ

SUMMARY

Eight cases of eosinophilic cellulitis are described with acute cutaneous swellings followed by indolent infiltration. The histology is distinctive with focal phagocytosis of eosinophilic material in the dermis. Occasionally these histological features are observed in other inflammatory dermatoses when eosinophils have infiltrated the connective tissue.





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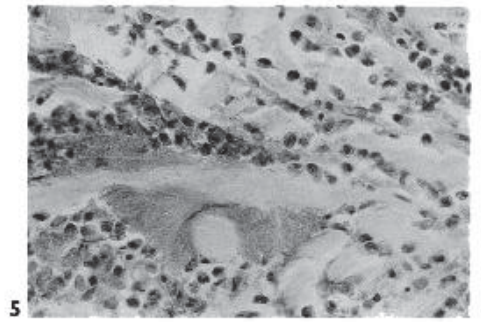

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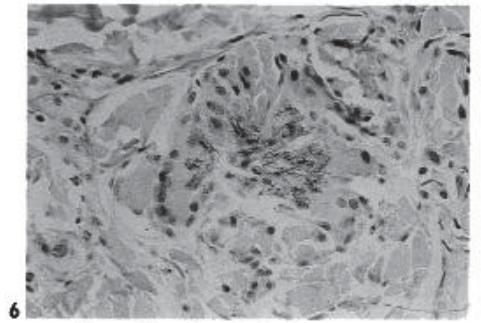

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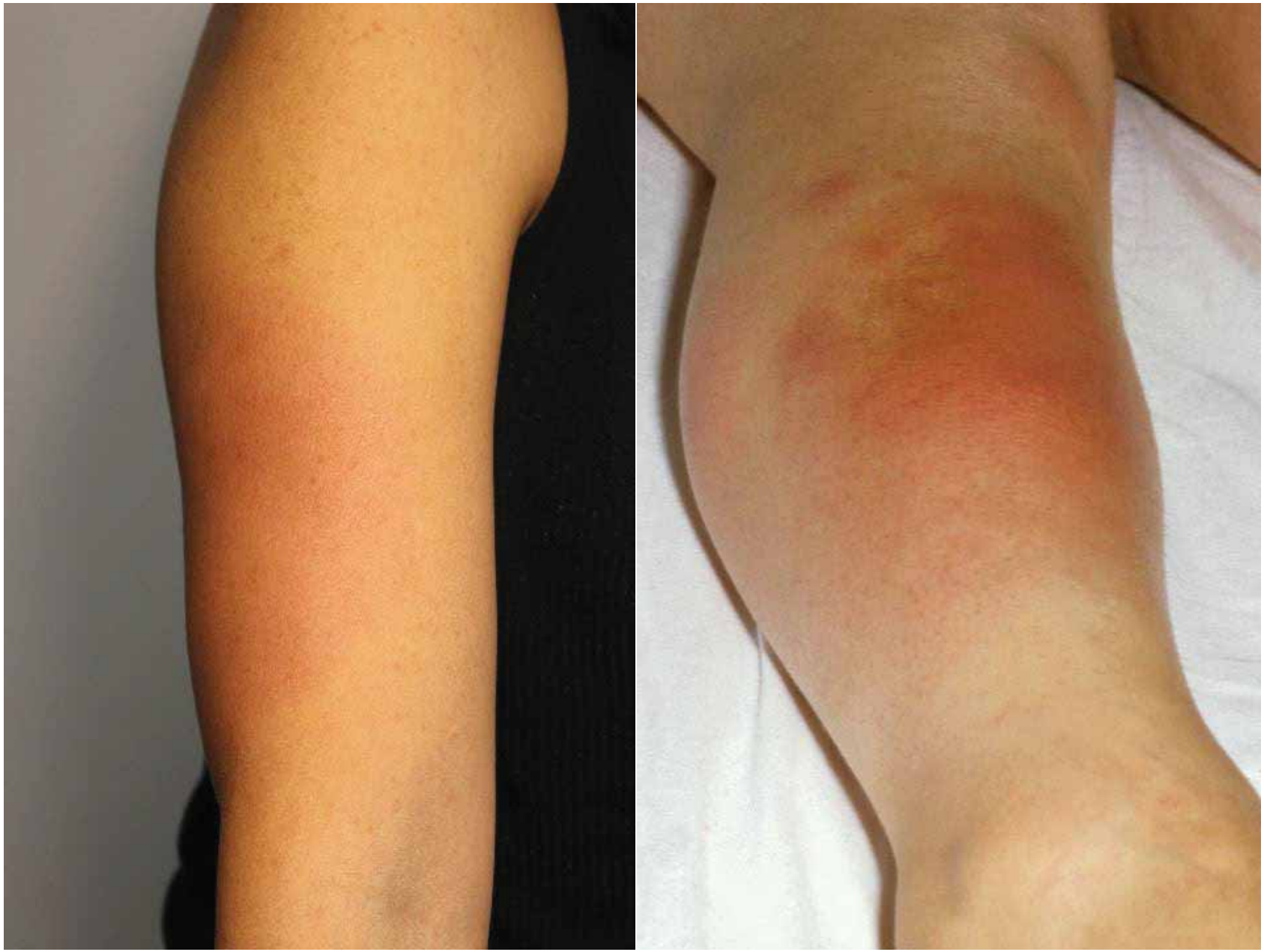
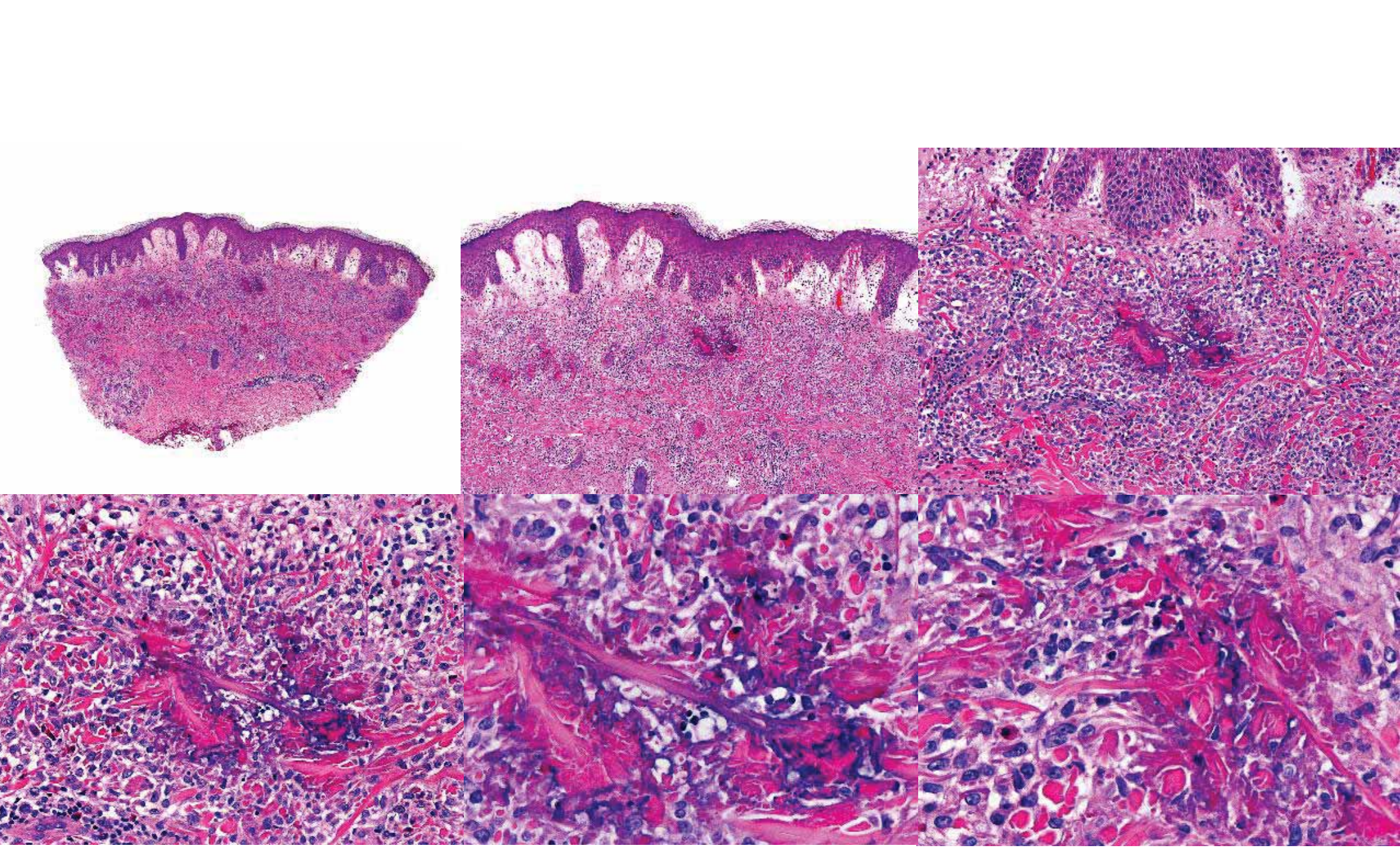
FIGURE 4. Scattered flame figures in dermis.
FIGURE 5. Collagen coated with eosinophilic material (early flame figure).
FIGURE 6. Phagocytosis in late flame figure.

Wells syndrome. Clinical features

- Recurrent episodes of itching or burning edematous plaques.
- Some plaques may have an annular or arcuate configuration.
- Vesicles and bullae may also be seen.
- The plaques become indurated and lesions resolve over 4 to 8 weeks.
- The extremities are more frequently affected.
- Unknown pathogenesis. Local hypersensitivy reaction due to different triggers: insect bites or stings, drugs, vaccinations, allergic contact dermatitis, underlying malignancy, fungal, viral or parasitic infections.





HISTOGENESIS OF EXTRAVASCULAR NECROTIZING GRANULOMA

Immunologic disorder

↓

Infiltrate of polymorphonuclear leukocytes

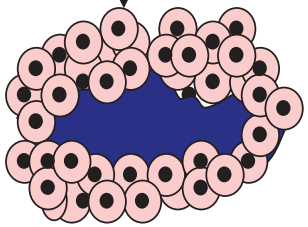
↓

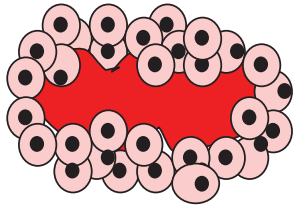
Release of lysosomal enzymes

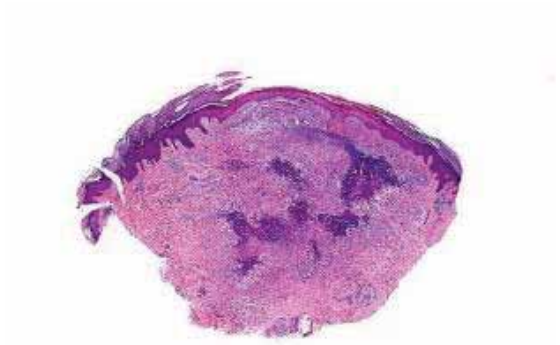
↓

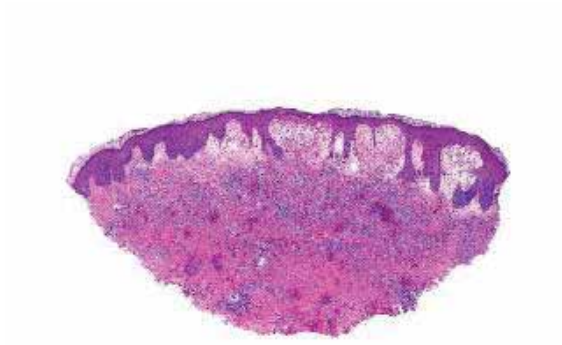
Collagen degeneration

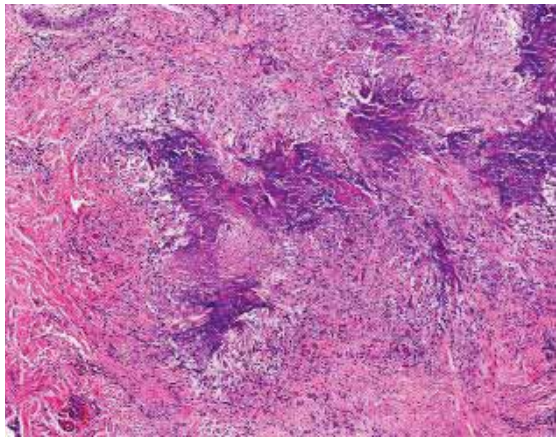
↙ ↘

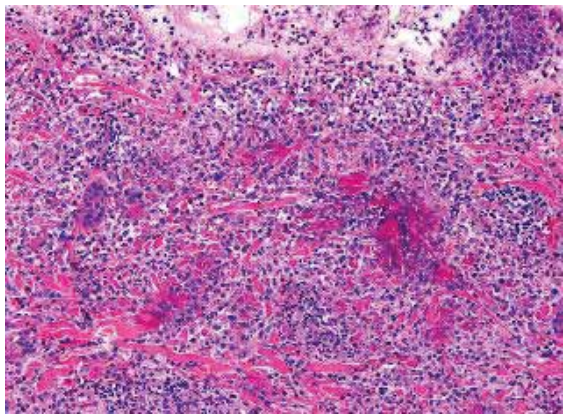
Neutrophils → Basophilic degeneration →  → Churg-Strauss granuloma or Winkelmann granuloma

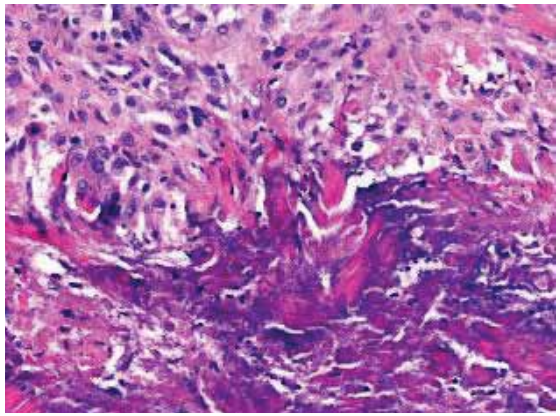
Eosinophils → Eosinophilic degeneration →  → Flame figures (Wells syndrome, insect bite, etc.)

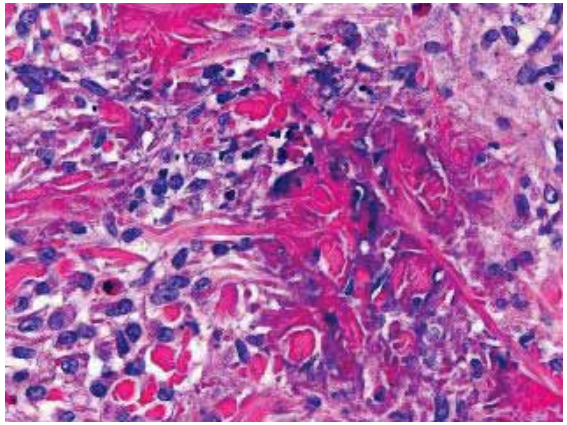




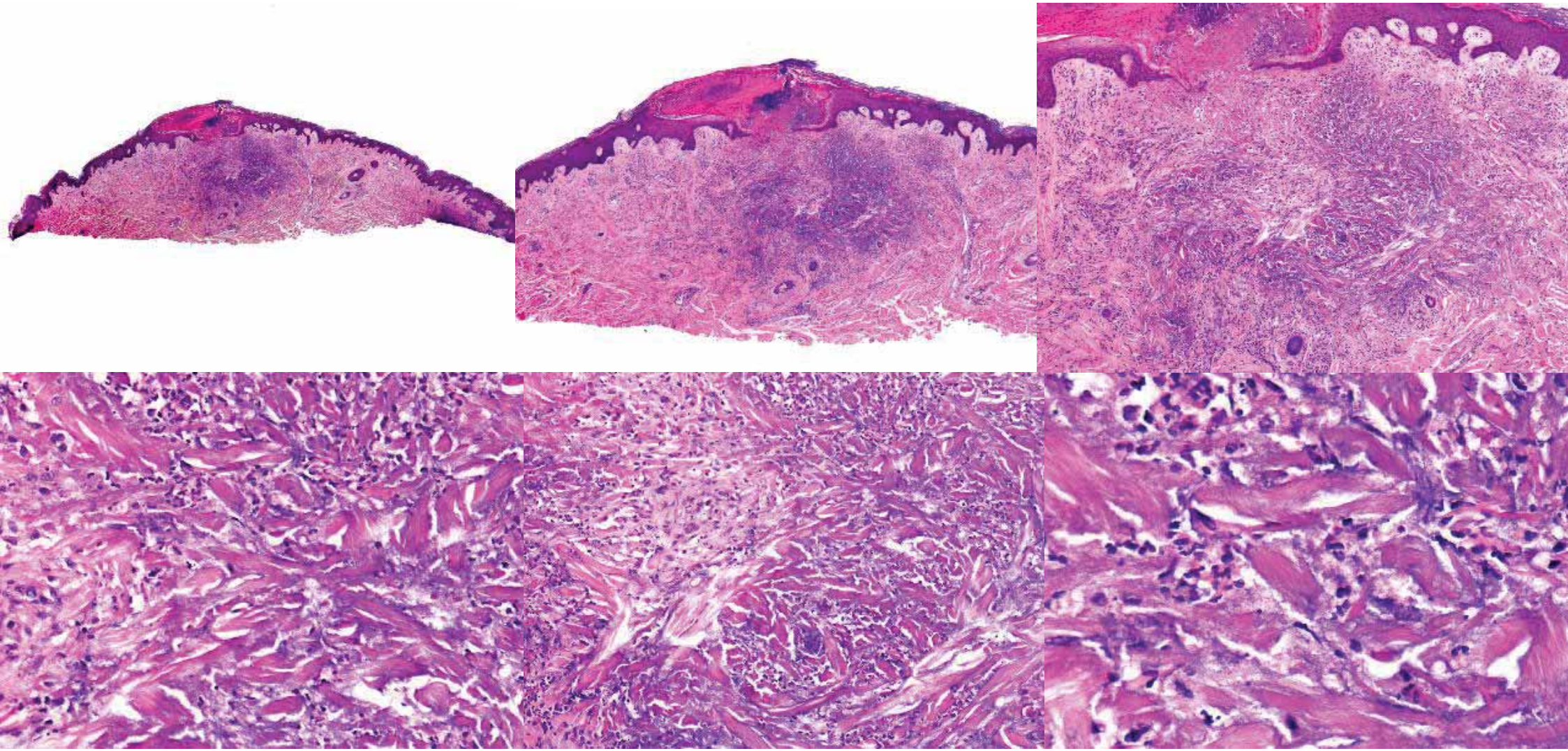








Sweet syndrome with Churg-Strauss granuloma



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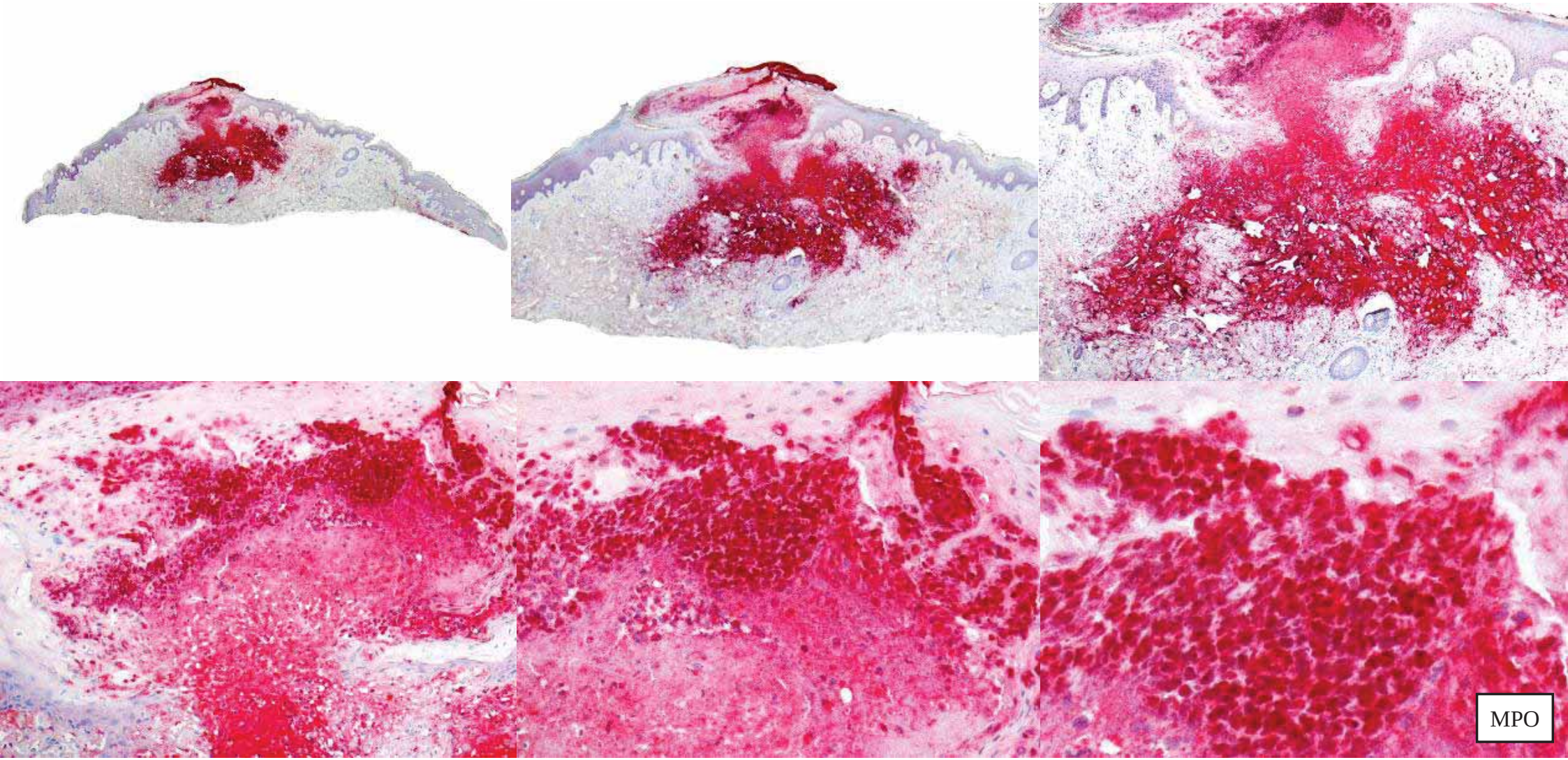

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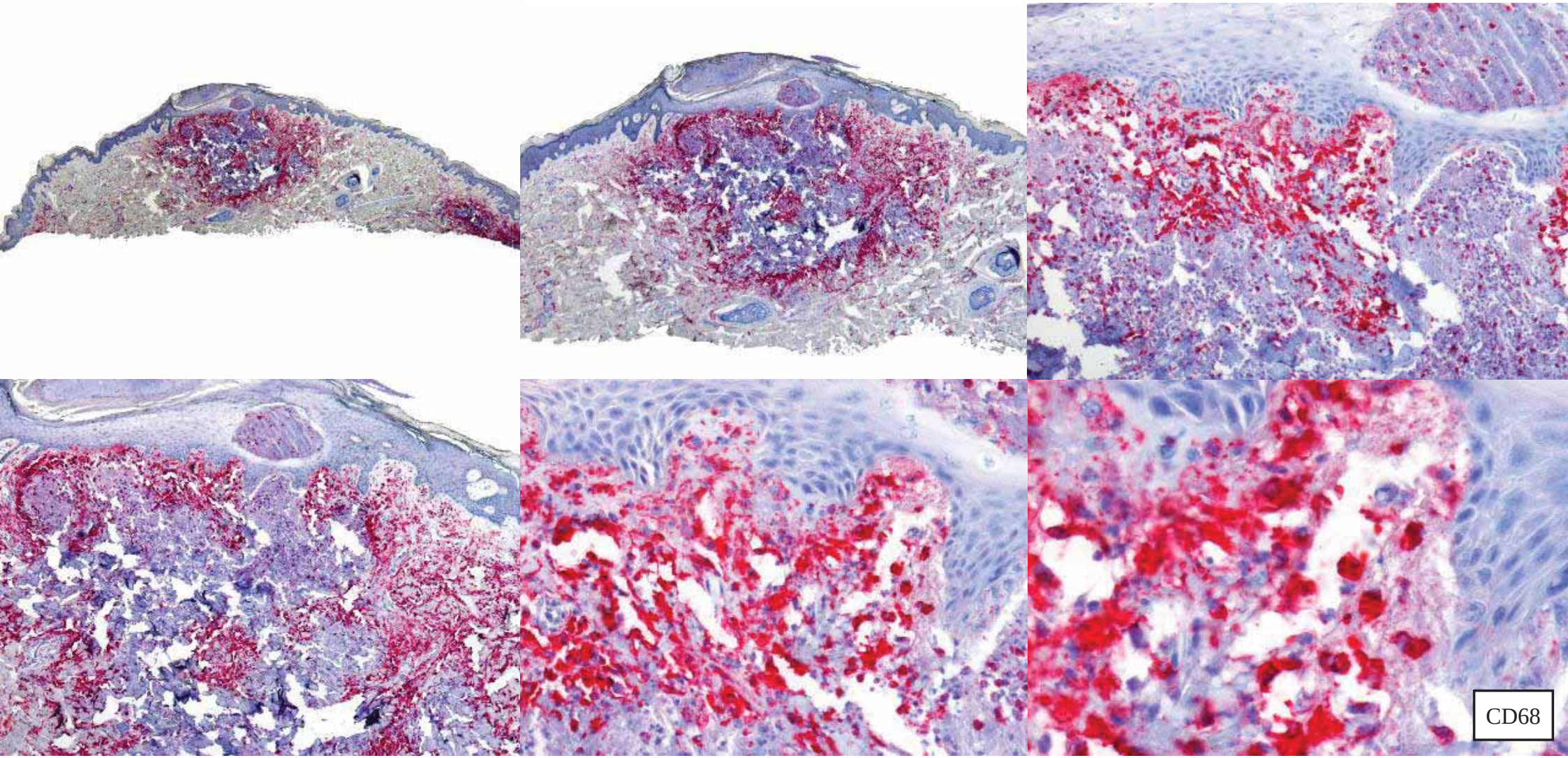
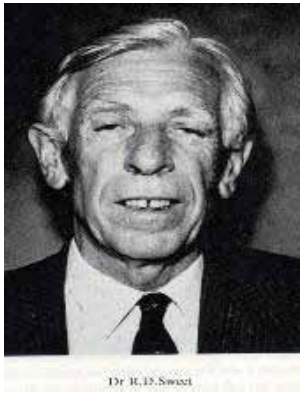
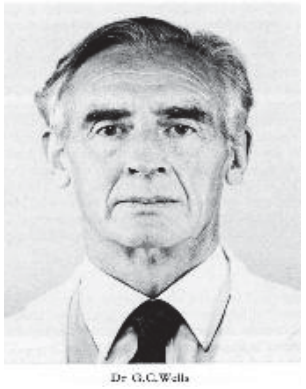




Dr R.D.Sweet



Dr G.C.Wells

Sweet syndrome	Wells syndrome
Fever (40-80%)	Fever (25%)
Erythematous-edematous plaques	Erythematous-edematous plaques
Blood leukocytosis	Blood eosinophilia
Edema of the papillary dermis	Edema of the papillary dermis
Neutrophilic dermal infiltrate	Eosinophilic dermal infiltrate
No vasculitis	No vasculitis
Churg-Strauss extravascular granuloma	Flamme figures
Rapid response to systemic corticosteroids	Rapid response to systemic corticosteroids
Reactive process: infections, malignant neoplasms, etc	Reactive process: infections, malignant neoplasms, etc

Personal approach

- Eosinophilic Sweet syndrome = Wells syndrome.

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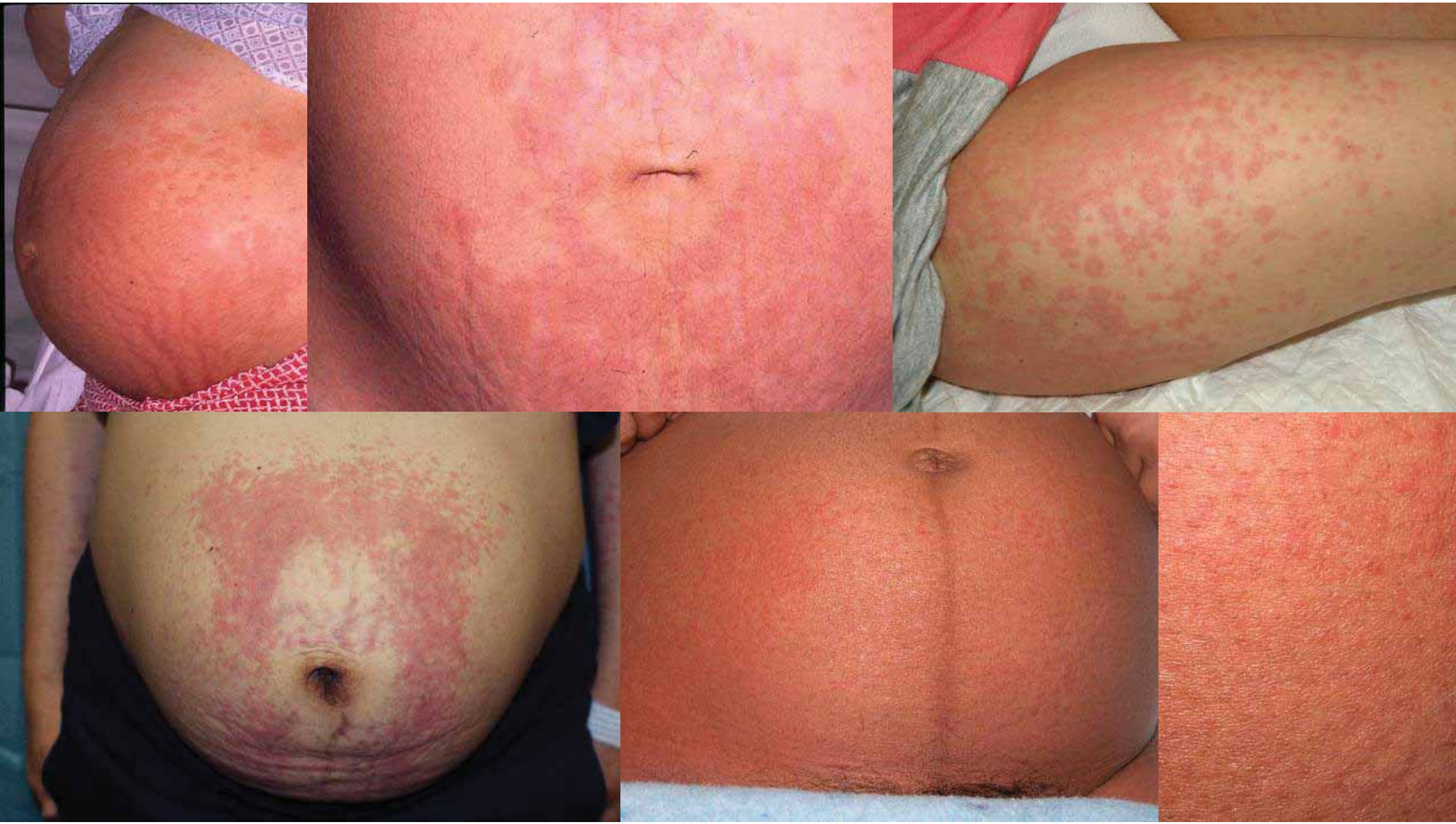
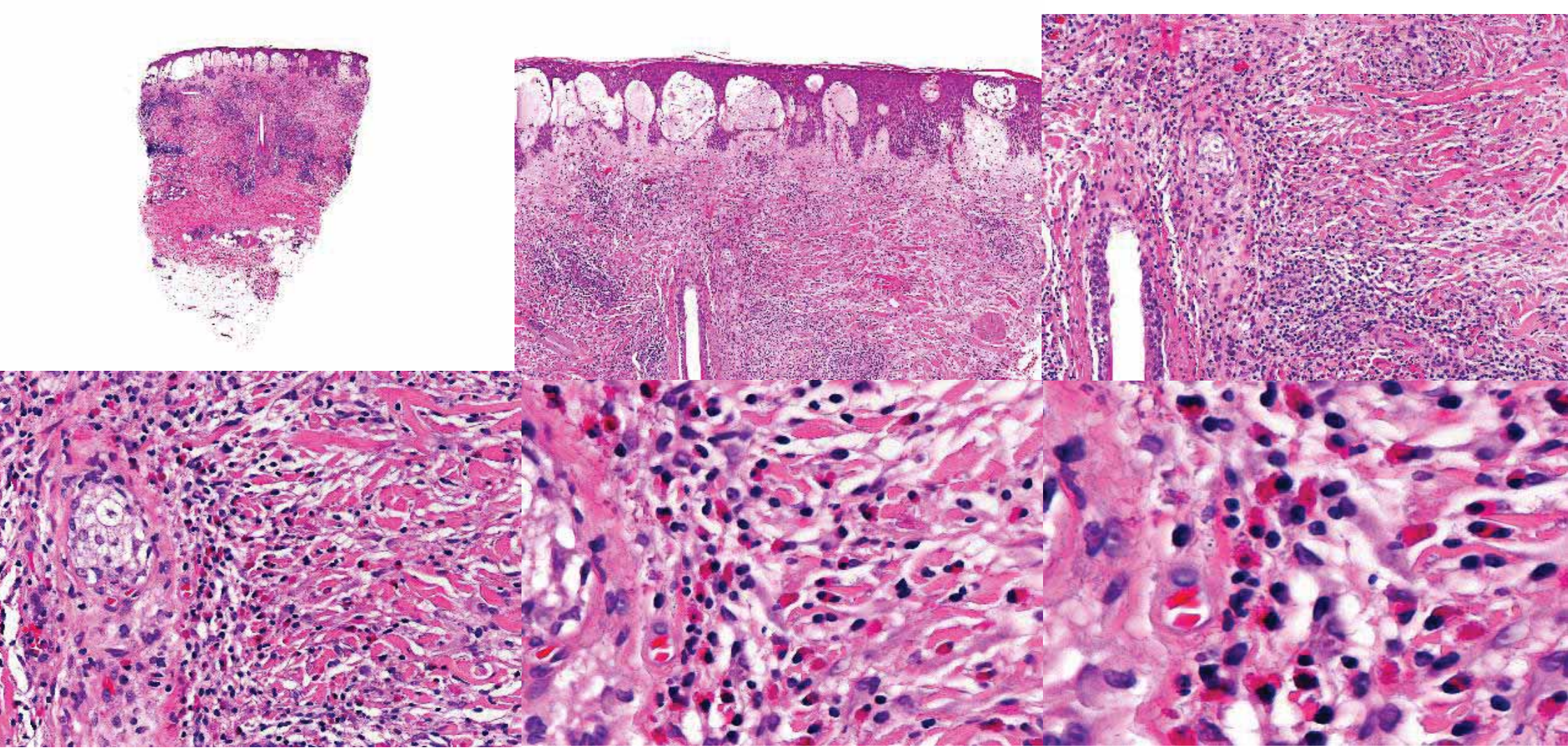
Polymorphic eruption of pregnancy

- Previously named PUPP: pruritic urticarial papules of pregnancy
- Polymorphic lesions: urticarial papules, vesicles, targetoid and eczematous lesions.
- Pruritic erythematous edematous papules and plaques that usually first appear within striae distensae of abdominal skin with periumbilical sparing during the latter period of the third trimester of pregnancy or immediately postpartum.
- Most frequent in primiparous women and usually does not recur in subsequent pregnancies.
- No maternal or fetal risk.





Polymorphic eruption of pregnancy (PEP)

Differential diagnosis with herpes gestationis (HG)

- Cutaneous lesions of HG appear earlier in pregnancy than those of PEP.
- Lesions of HG involve periumbilical skin and show no predilection by striae distensae, whereas those of PEP spare periumbilical region and tend to develop on striae distensae.
- HG recurs in subsequent pregnancies, whereas PEP does not recur.
- DIF and IIF studies in HG demonstrate linear deposition of IgG and C3, whereas in PEP these studies are negative.

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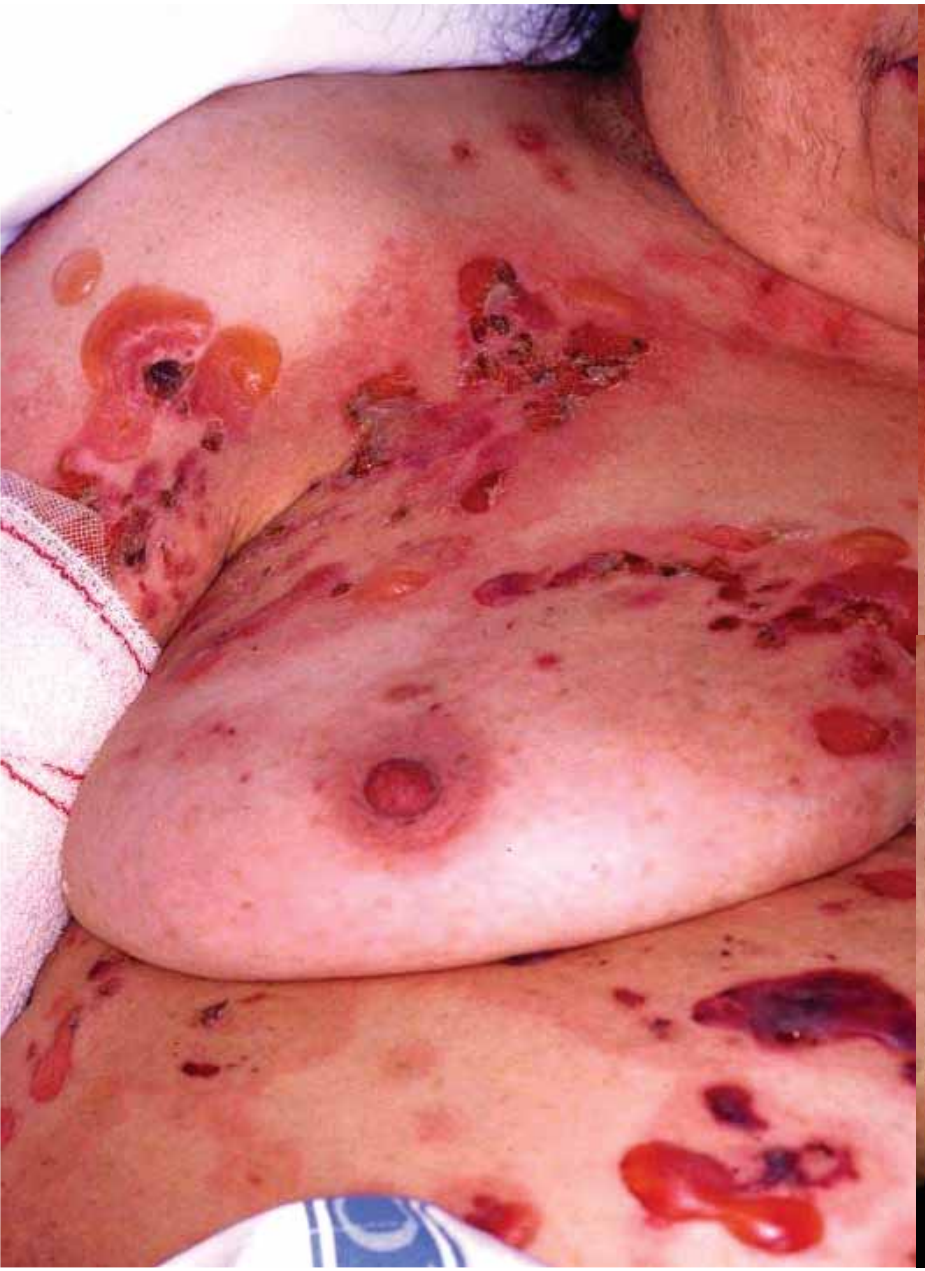
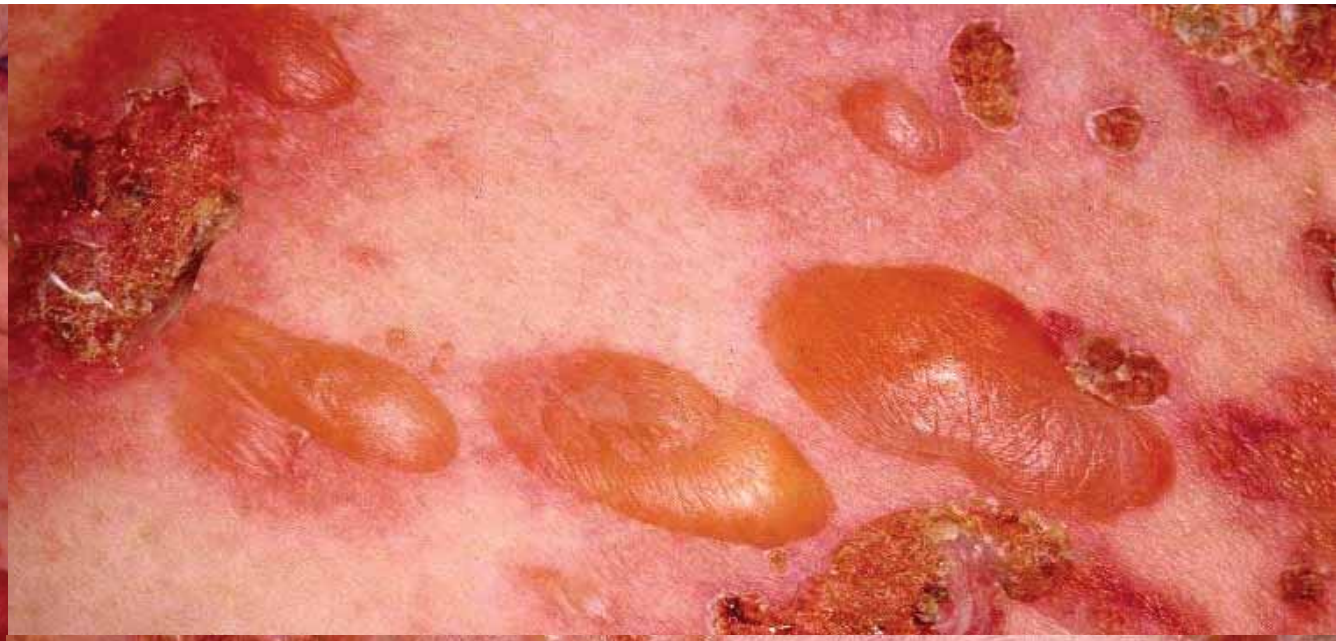
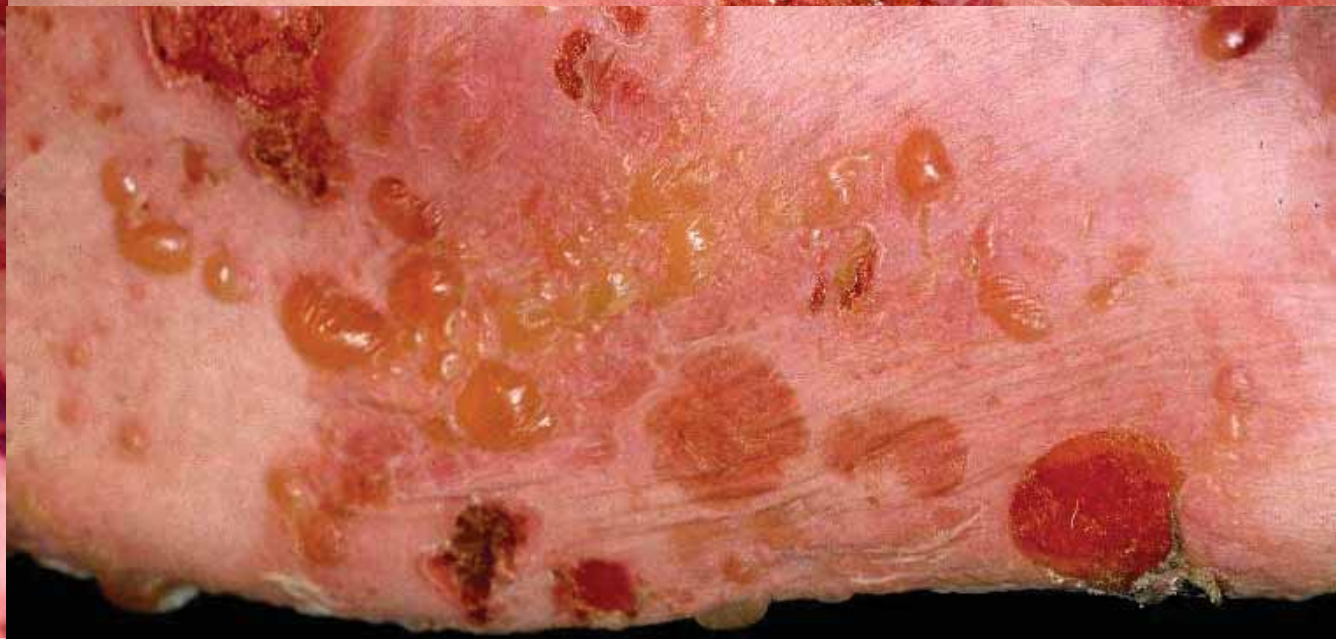
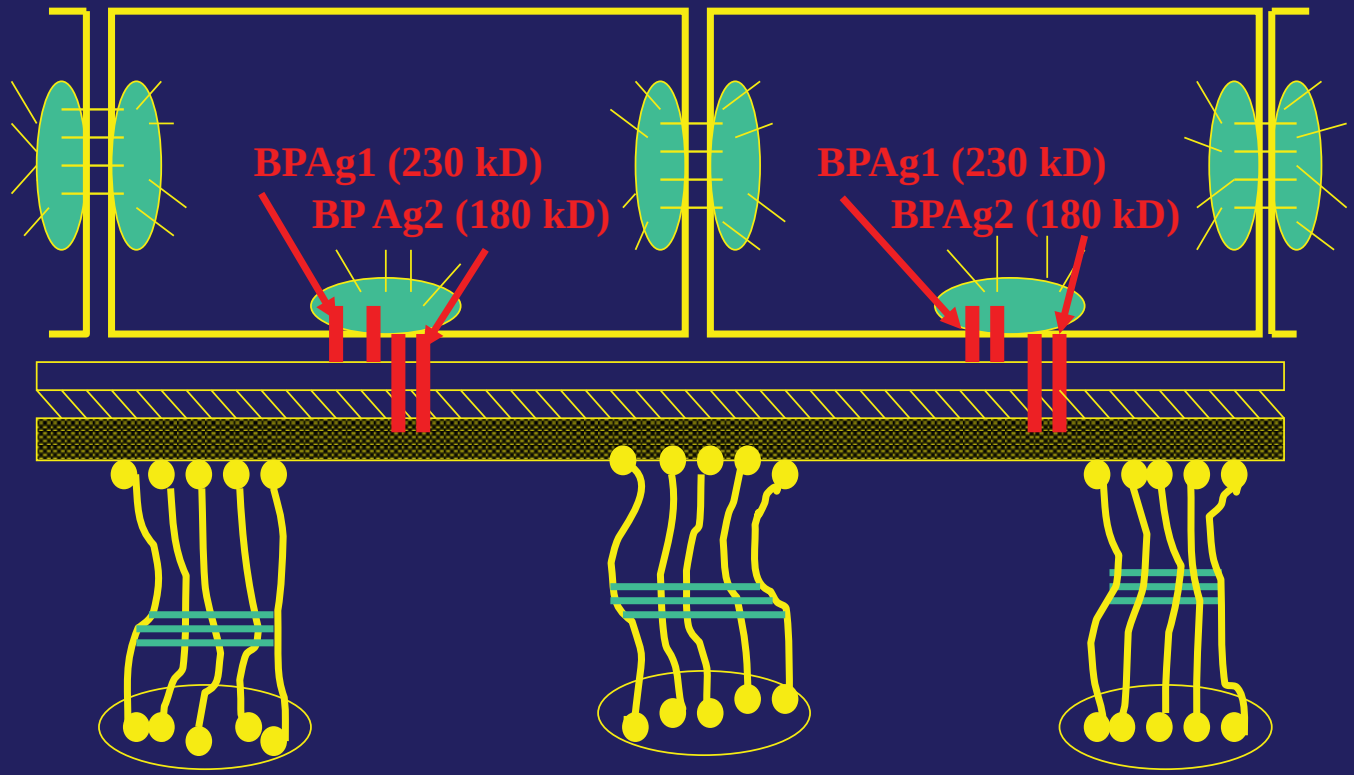
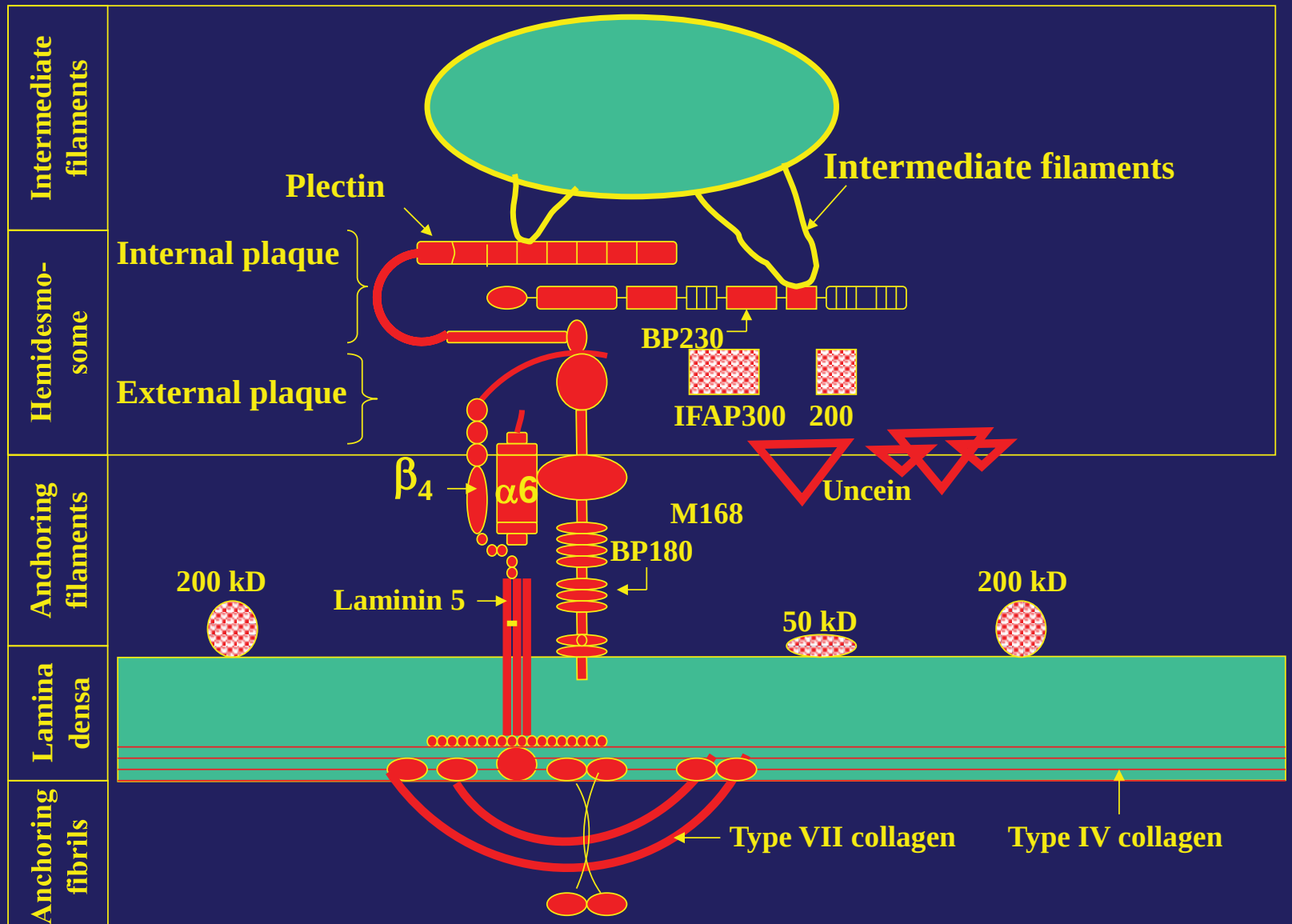


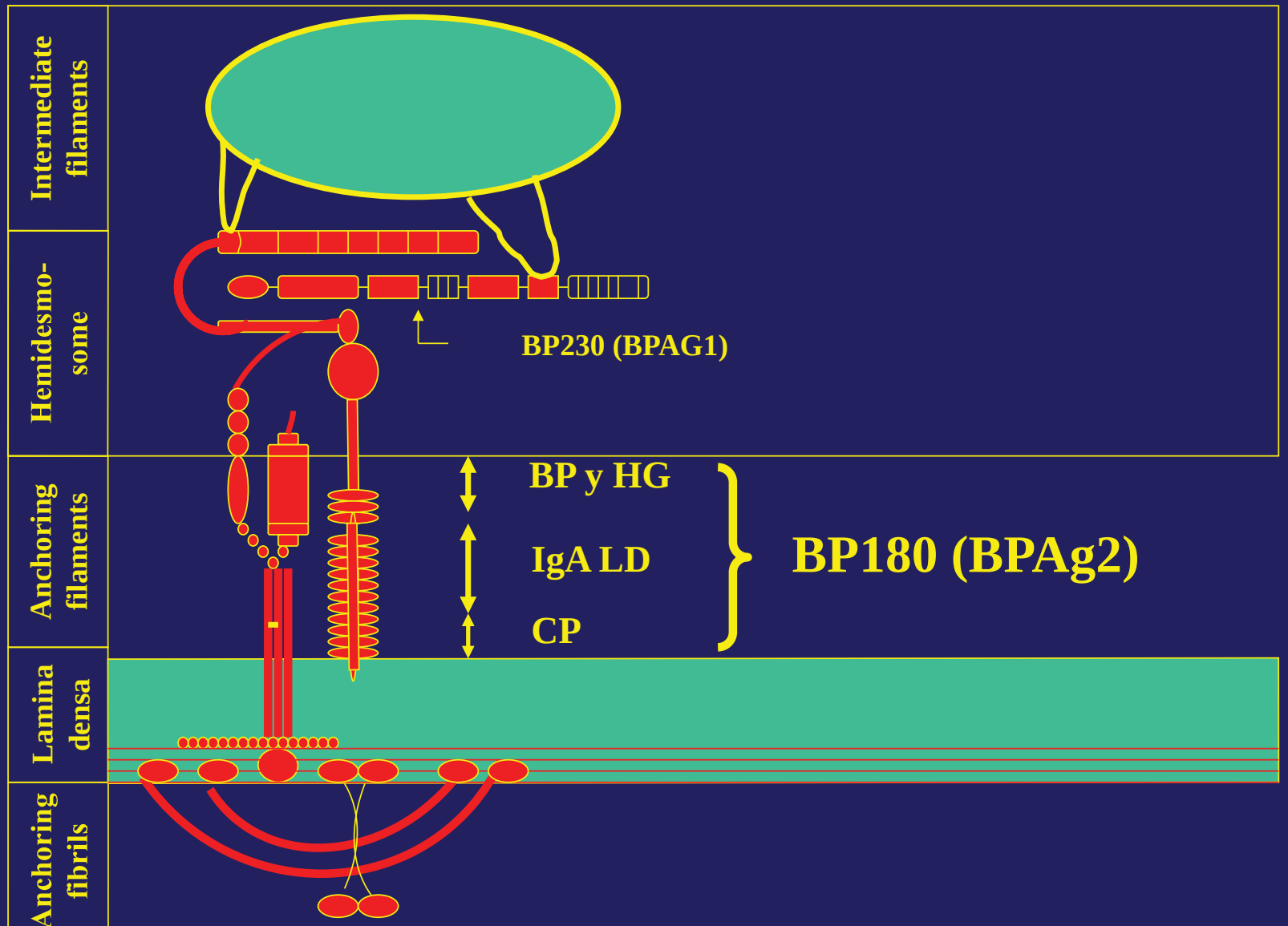


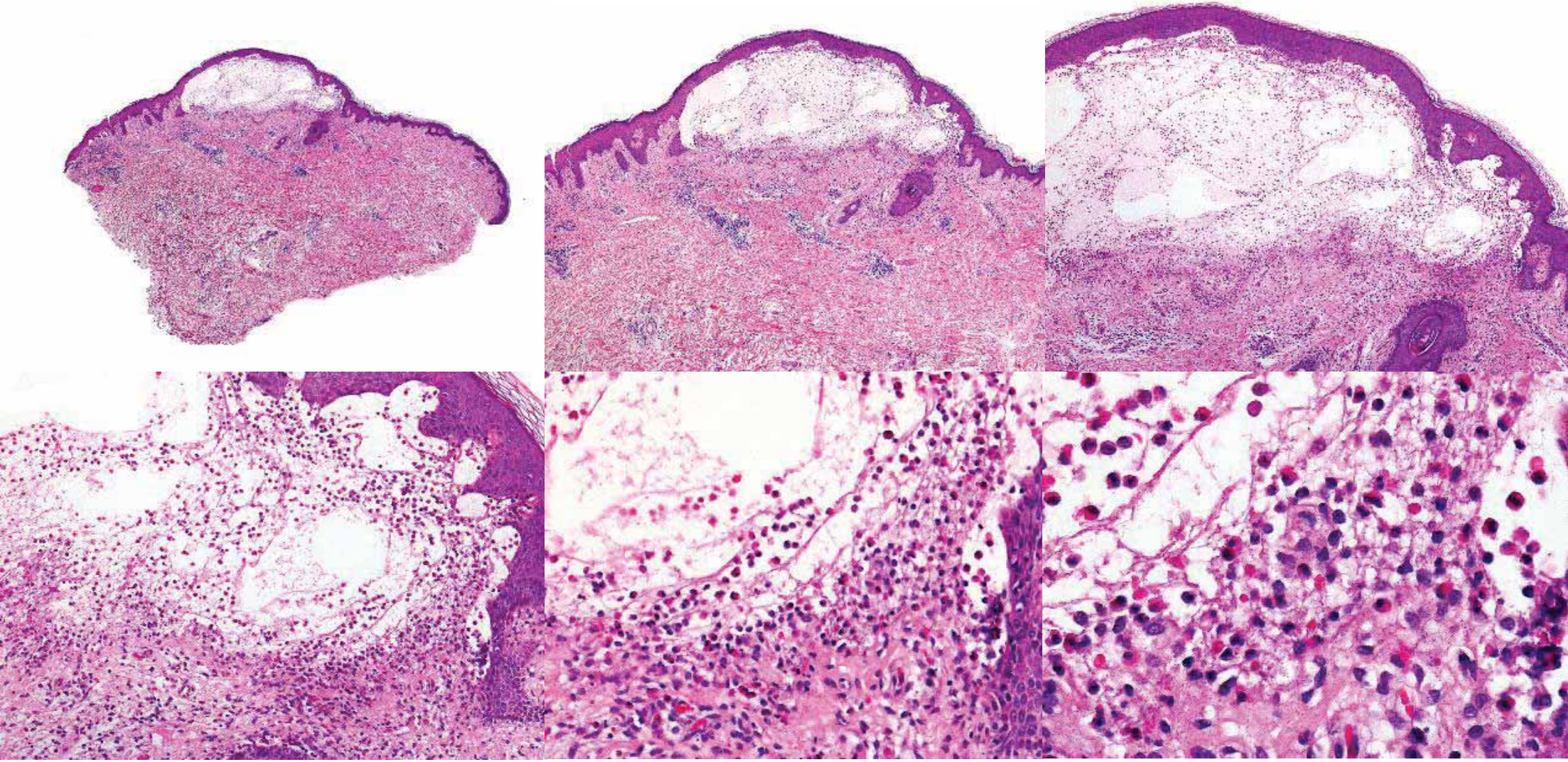


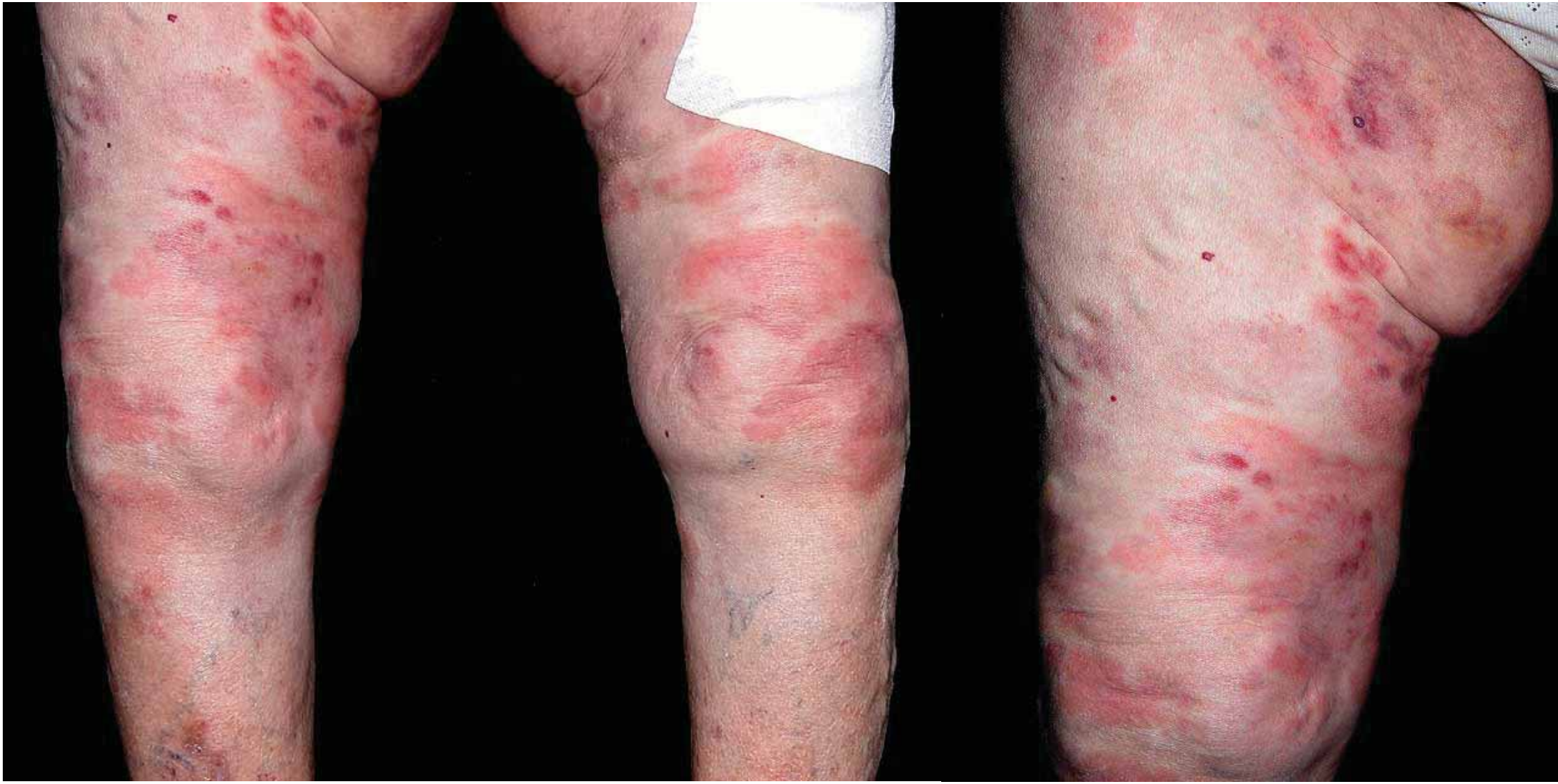
BULLOS PEMPHIGOID

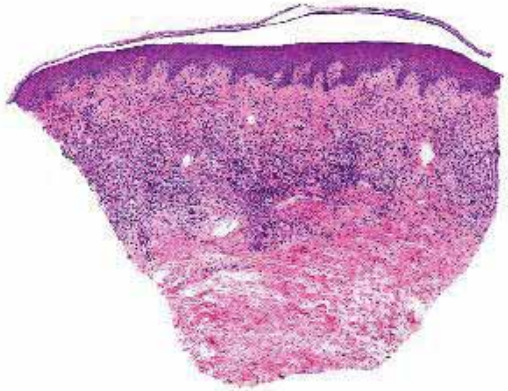
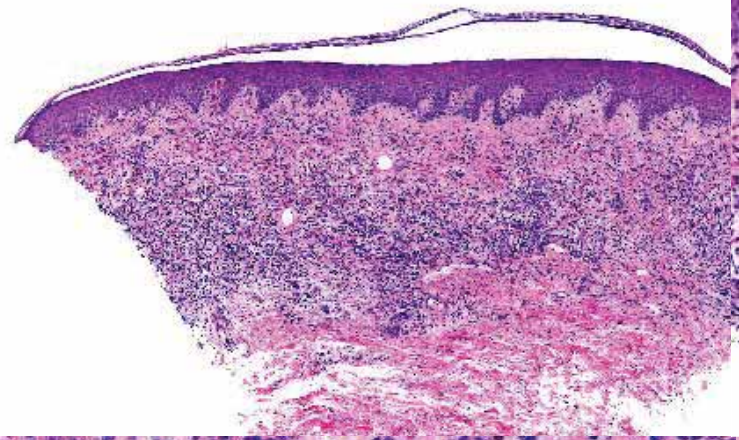
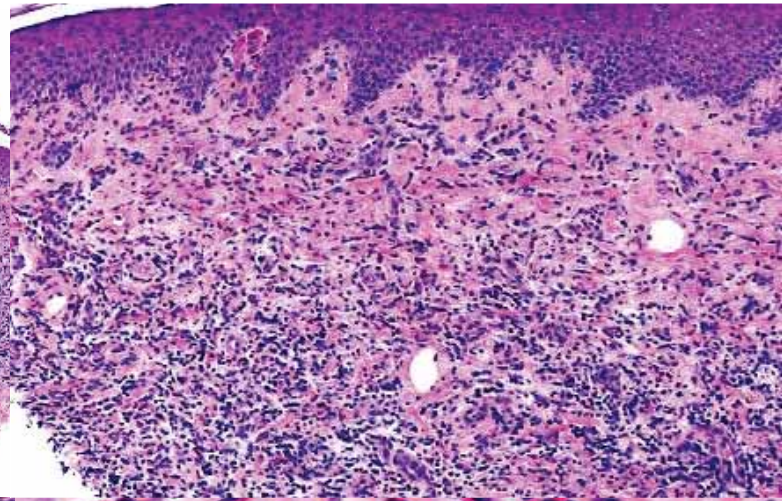
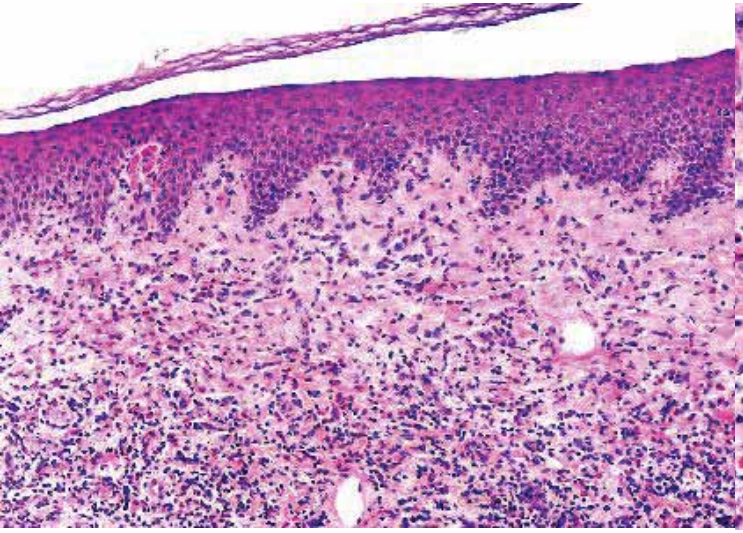
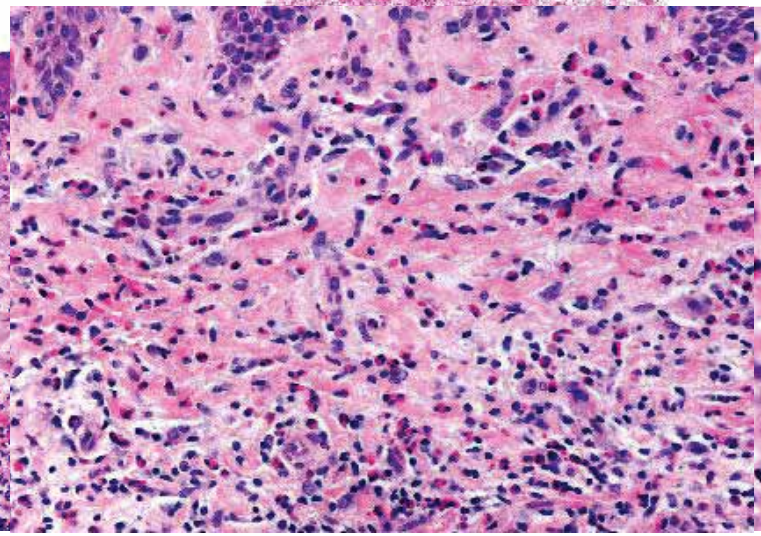
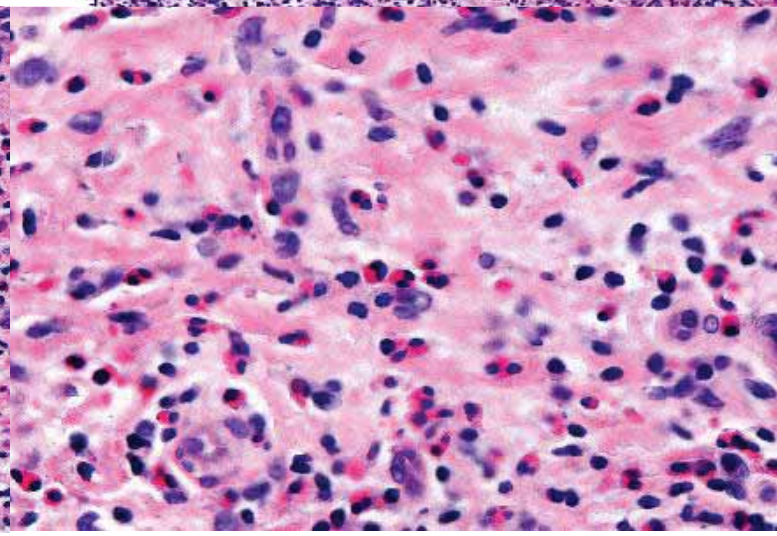


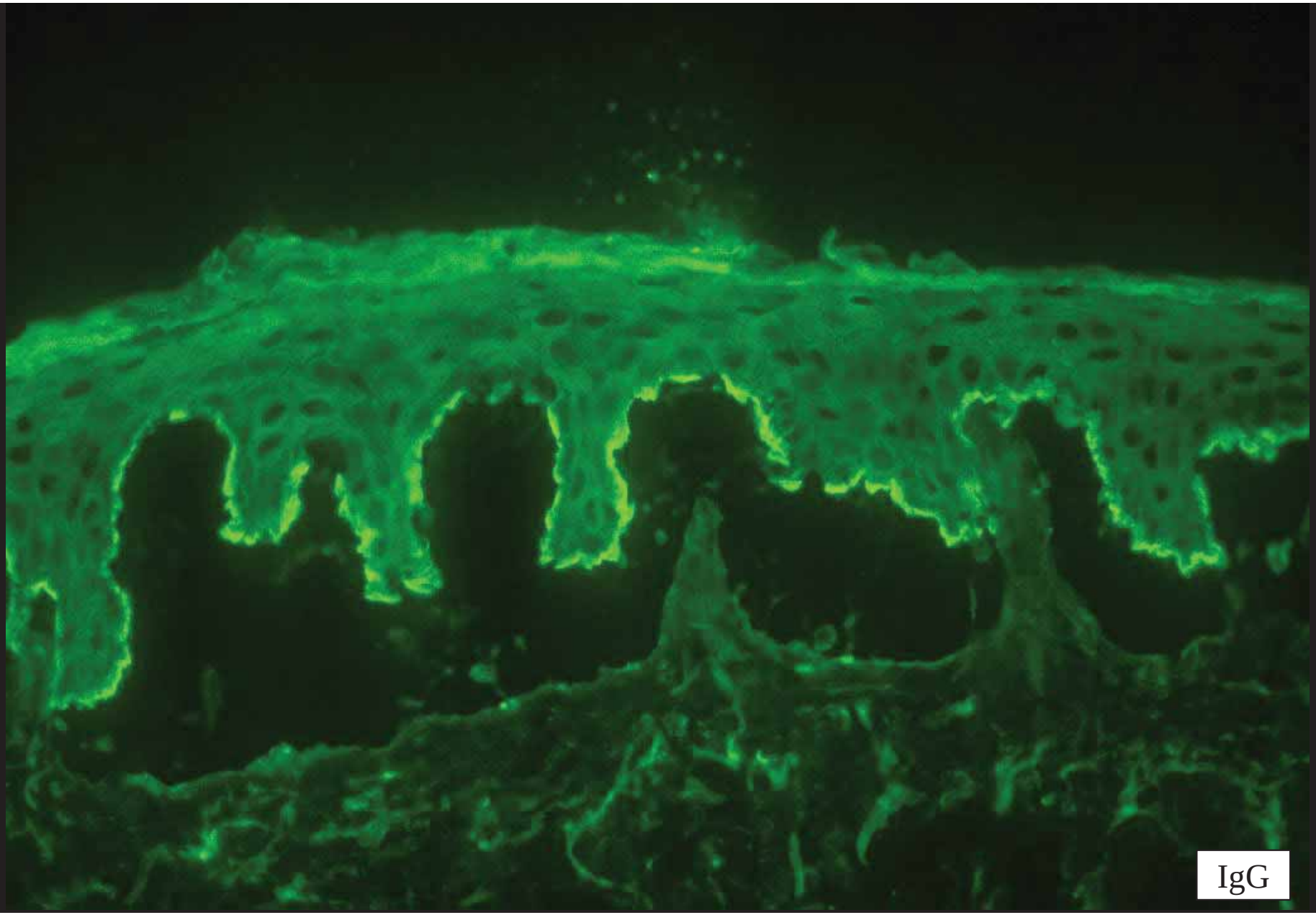

Intermediate filaments
Hemidesmo-some
Anchoring filaments
Lamina densa
Anchoring fibrils
Plectin
Intermediate filaments
Internal plaque
External plaque
BP230
IFAP300
200
Uncein
β4
α6
M168
BP180
Laminin 5
200 kD
200 kD
50 kD
Type VII collagen
Type IV collagen

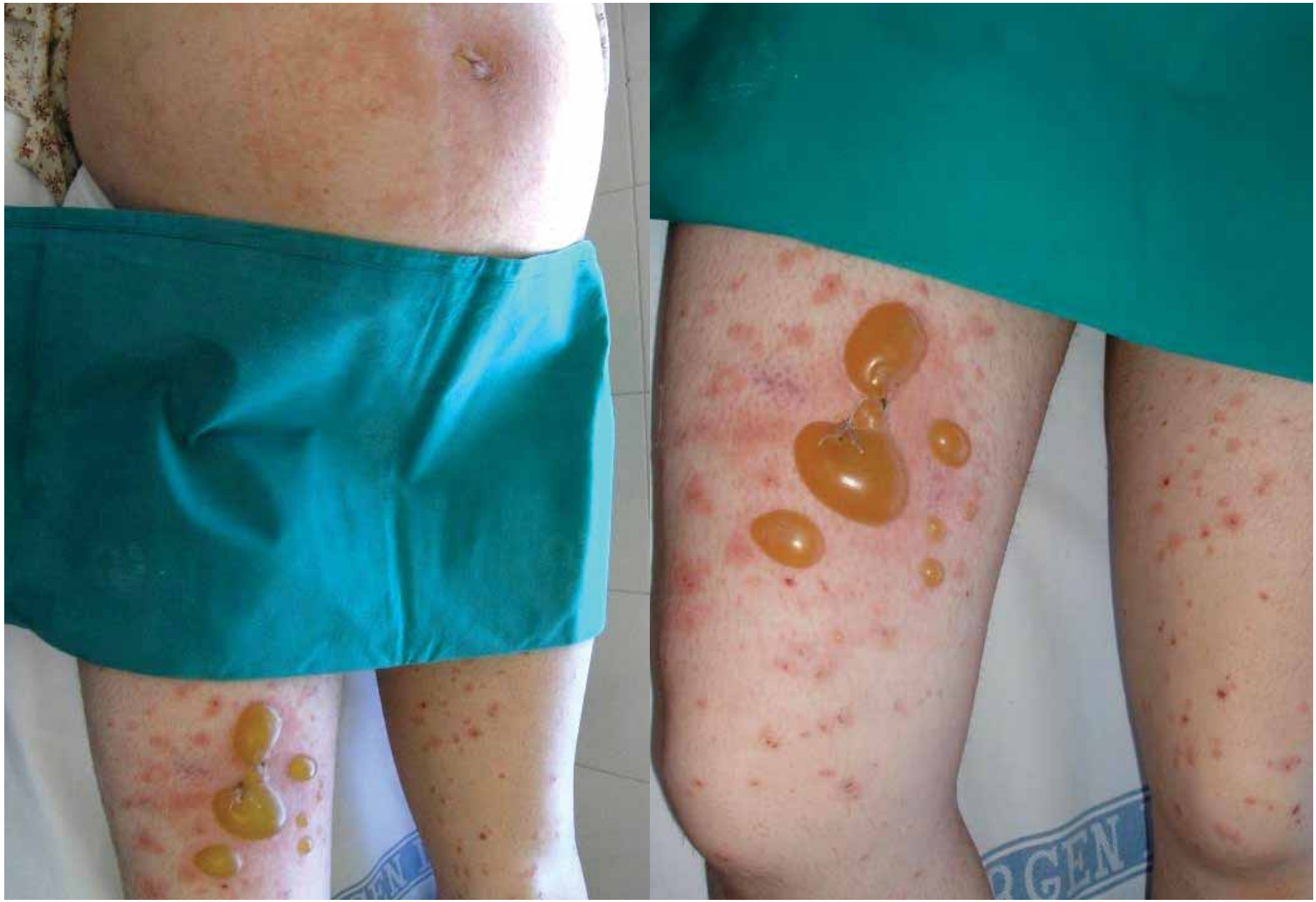

Intermediate filaments
Hemidesmo-some
Anchoring filaments
Lamina densa
Anchoring fibrils
BP230 (BPAG1)
BP y HG
IgA LD
CP
BP180 (BPAg2)

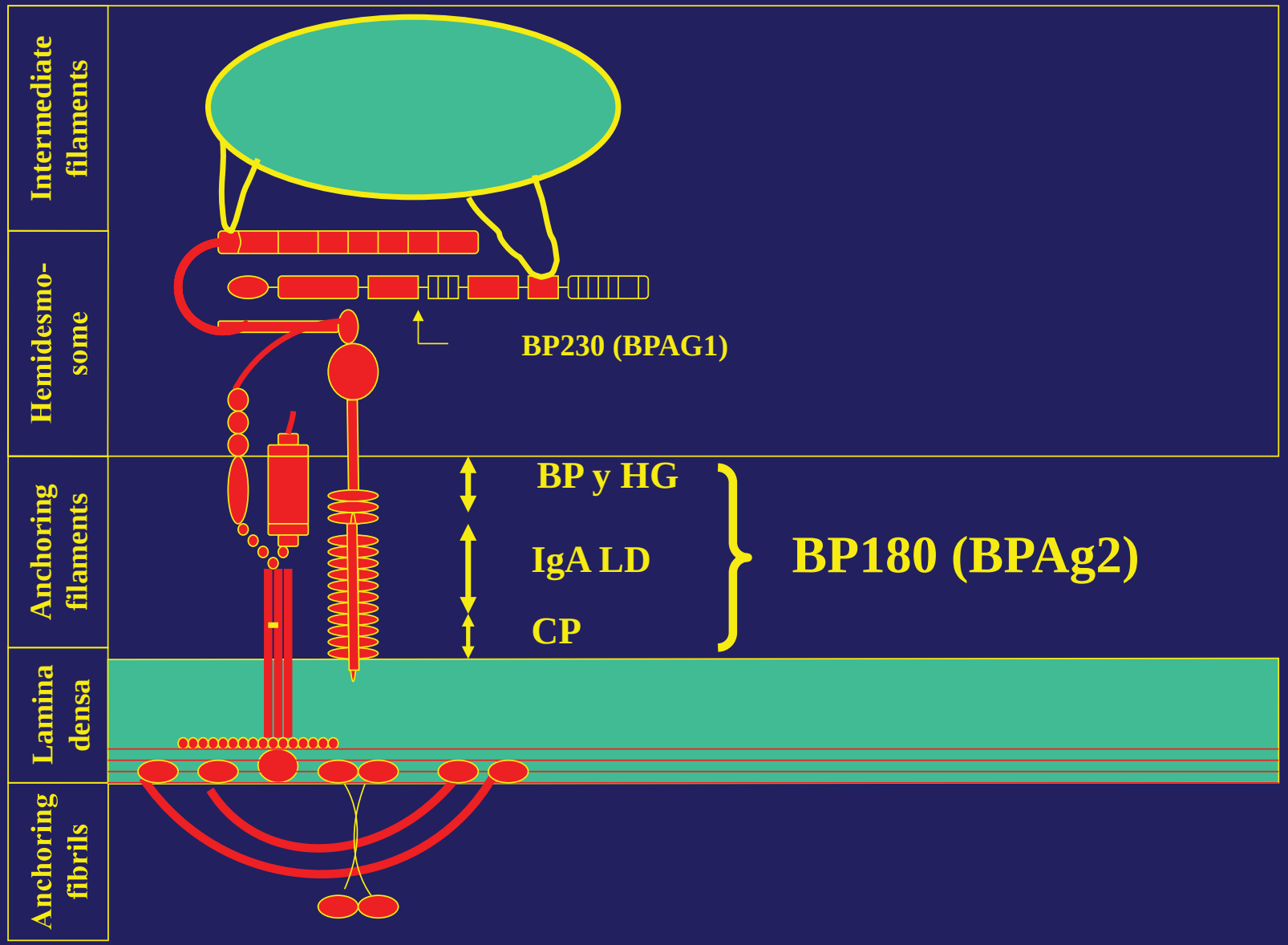


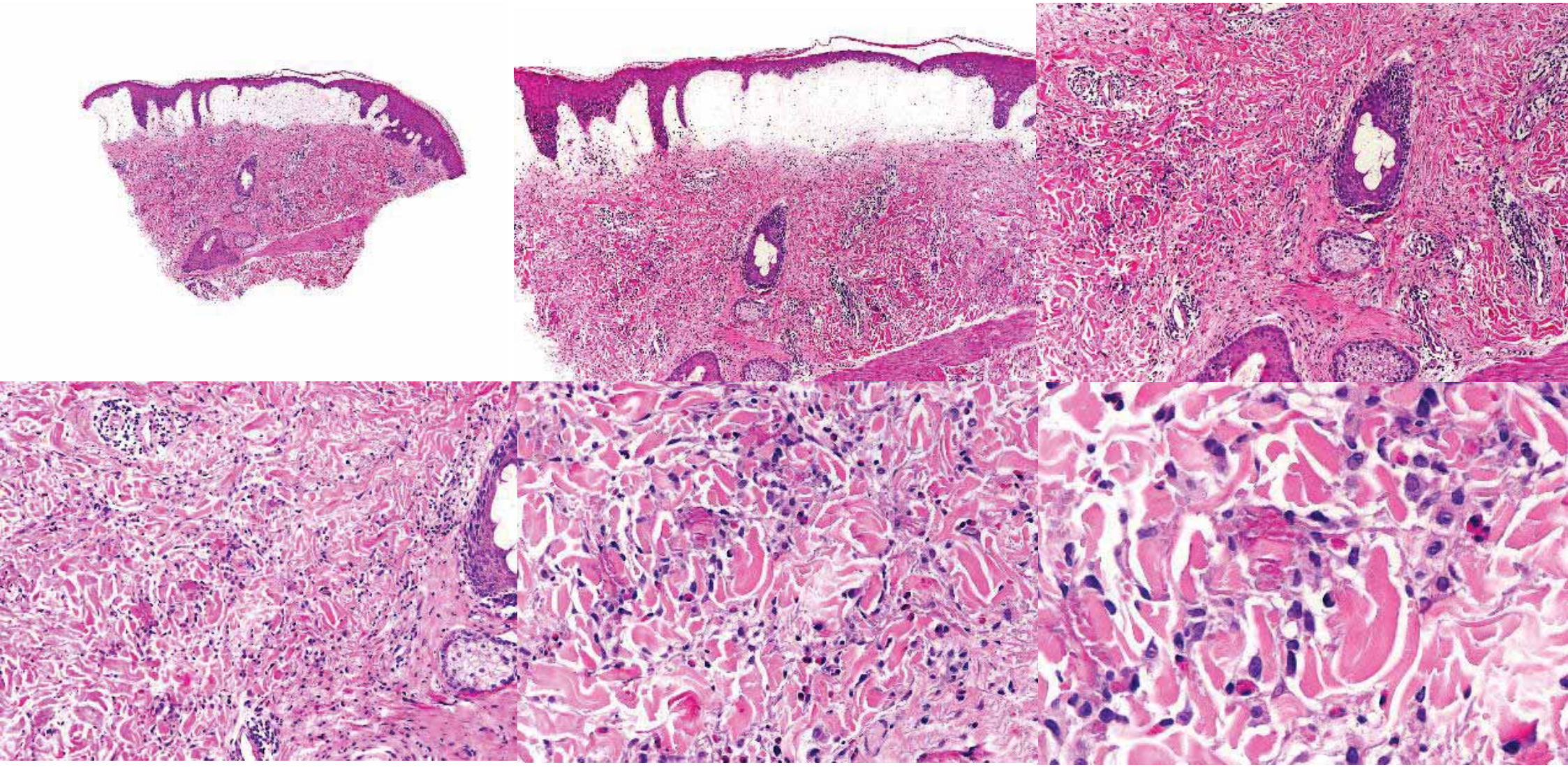


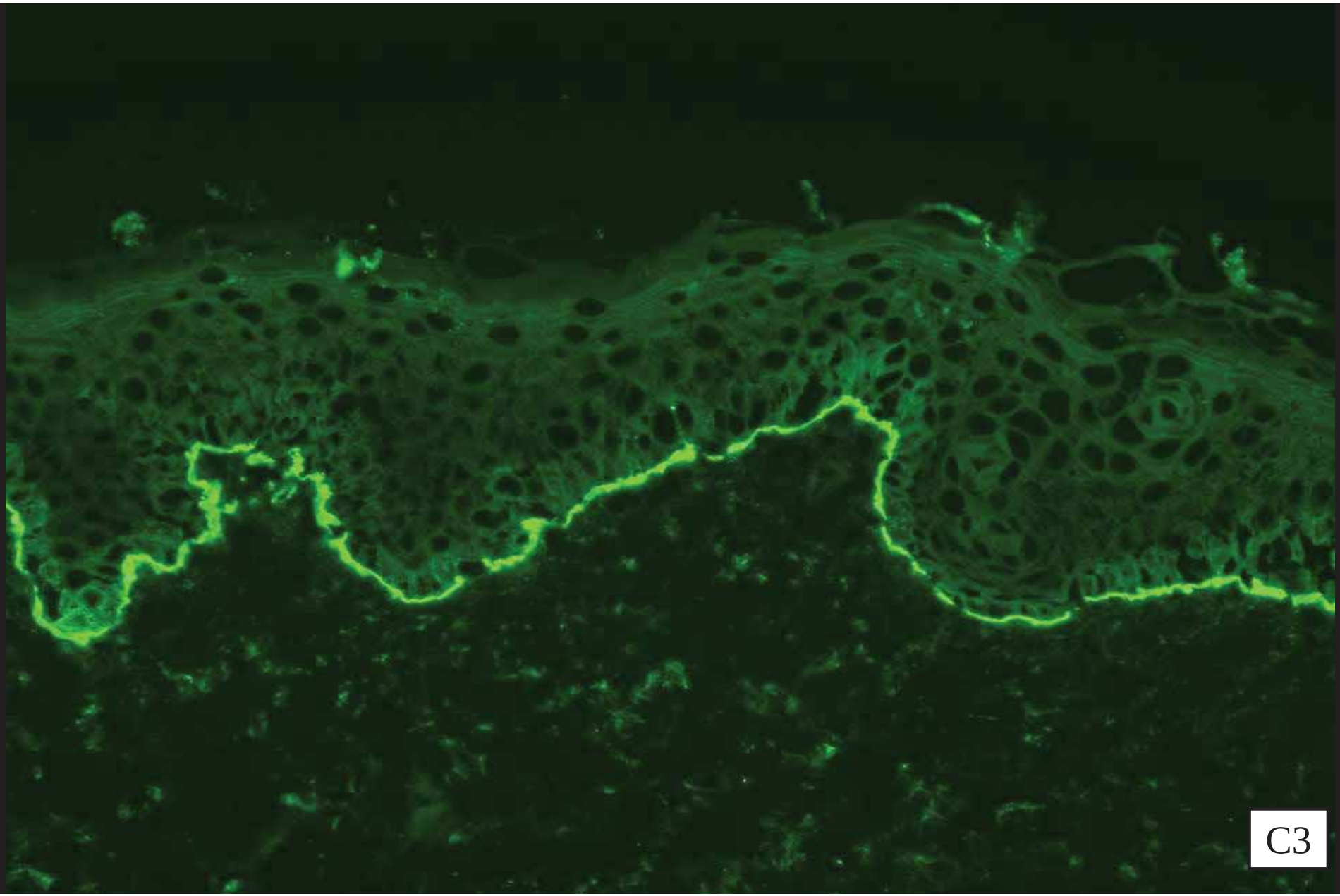








IgG




Intermediate filaments
Hemidesmo-some
Anchoring filaments
Lamina densa
Anchoring fibrils
BP230 (BPAG1)
BP y HG
IgA LD
CP
BP180 (BPAg2)

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The Journal of Dermatology

ORIGINAL ARTICLE

Tissue Eosinophil Counts: A Promising Marker for Optimizing Omalizumab Treatment in Bullous Pemphigoid

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ABSTRACT

Bullous pemphigoid (BP) is the most common autoimmune blistering disease, predominantly affecting the elderly. Current treatments rely mainly on corticosteroids and immunosuppressive agents but are often limited by significant side effects. Omalizumab, an anti-IgE monoclonal antibody, has emerged as a promising off-label therapy for BP, but predictive markers for treatment response remain poorly understood. This study evaluates the efficacy and safety of omalizumab in BP and explores potential predictors of response, with a focus on tissue eosinophil counts. A retrospective analysis of 27 patients with severe BP treated with omalizumab was conducted. Complete remission (CR) was achieved in 63% of patients, partial remission (PR) in 18.5%, and no response/flare up in 18.5%. The median total number of omalizumab doses was six (range 6–12), and 70.4% of patients received biweekly dosing. Notably, responders had significantly higher median tissue eosinophil counts ($p = 0.040$) than non-responders. No significant correlation was observed between treatment response and variables such as age, gender, disease duration, or blood eosinophil counts. Our findings suggest that tissue eosinophil levels may serve as a reliable predictor of omalizumab response in BP ($Z = -2.034$, $p = 0.040$). Omalizumab demonstrated significant efficacy with minimal adverse effects, as only one patient reported a mild side effect (tickling sensation in the throat). While the study's single-center design and small sample size limit generalizability, it provides valuable insights into potential predictive markers and supports omalizumab as a safe and effective treatment option for BP.

1 | Introduction

Bullous pemphigoid (BP) is the most common autoimmune blistering disorder that primarily impacts the elderly population, and its occurrence is escalating due to longer life spans [1]. It presents as erythematous or urticarial patches or plaques on the skin, typically with intense pruritus, followed by tense blisters and blisters on the base of urticarial erythema [2]. The prevalence of BP is approximately 34.2% per million individuals without favoring any gender. Meanwhile, annual mortality rates vary between 11% and 41% in different countries [3, 5].

Bullous pemphigoid occurs due to autoantibodies targeting two structural components of hemidesmosomes, namely BP180 (BPAG2) and/or BP230 (BPAG1). These autoantibodies are classically of the IgG type (usually IgG4), but recent studies have shown that IgE autoantibodies are also detectable in at least 75% of untreated BP patients, and autoreactive IgE-mediated inflammation has been shown to contribute to the pathogenesis of BP [4].

The treatment of BP currently relies mainly on corticosteroids, administered either topically or systemically, often in combination with antibiotics and immunosuppressive agents [2]. Despite advancements in treatment, the management of severe BP remains challenging due to the long-term side effects of corticosteroids, such as weight gain, hypertension, osteoporosis, and cataract [2]. Omalizumab, an anti-IgE monoclonal antibody,

Notably, responders had significantly higher median tissue eosinophil counts ($p = 0.040$) than non-responders.

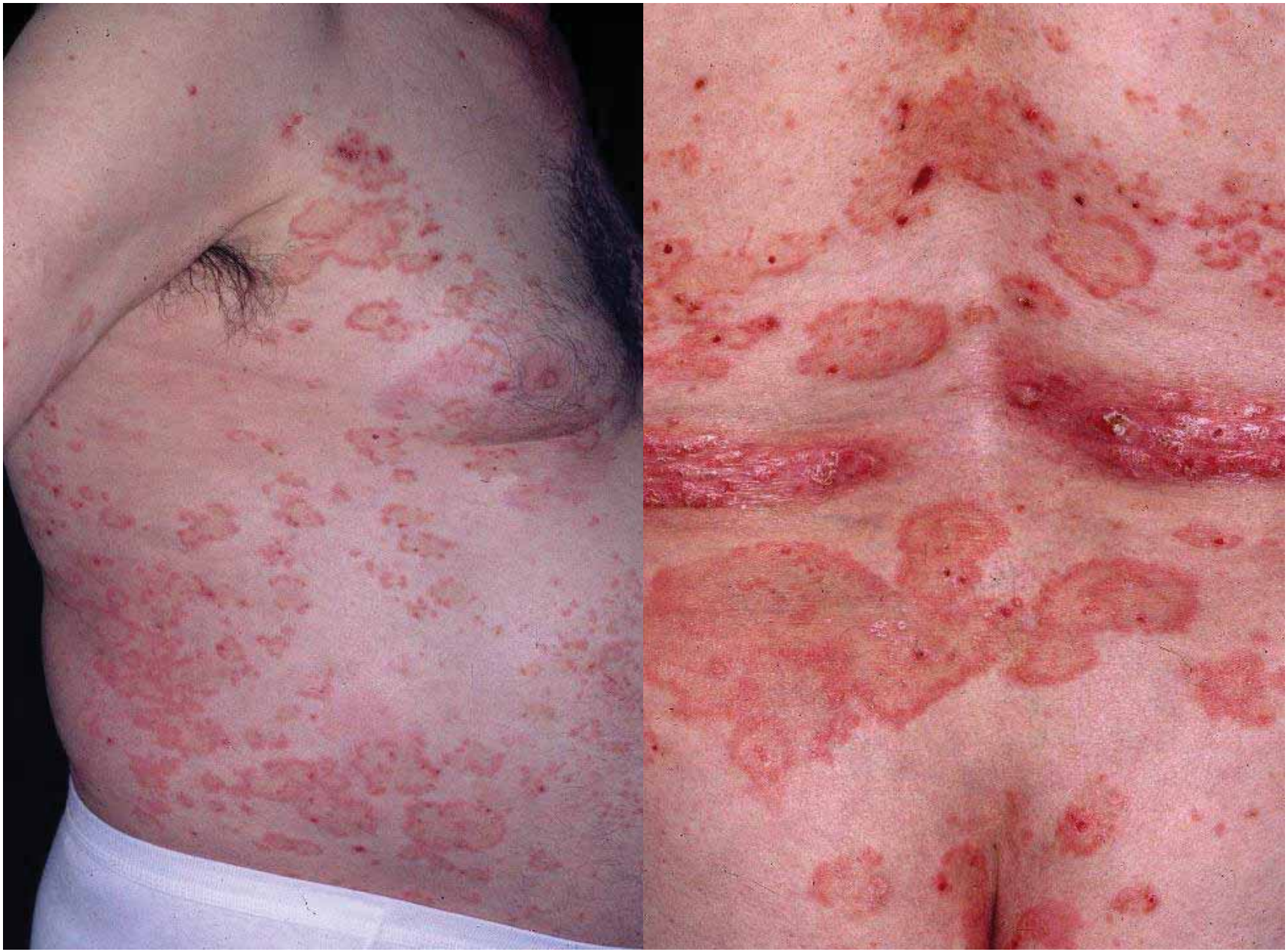
EOSINOPHILIC DERMATOSES

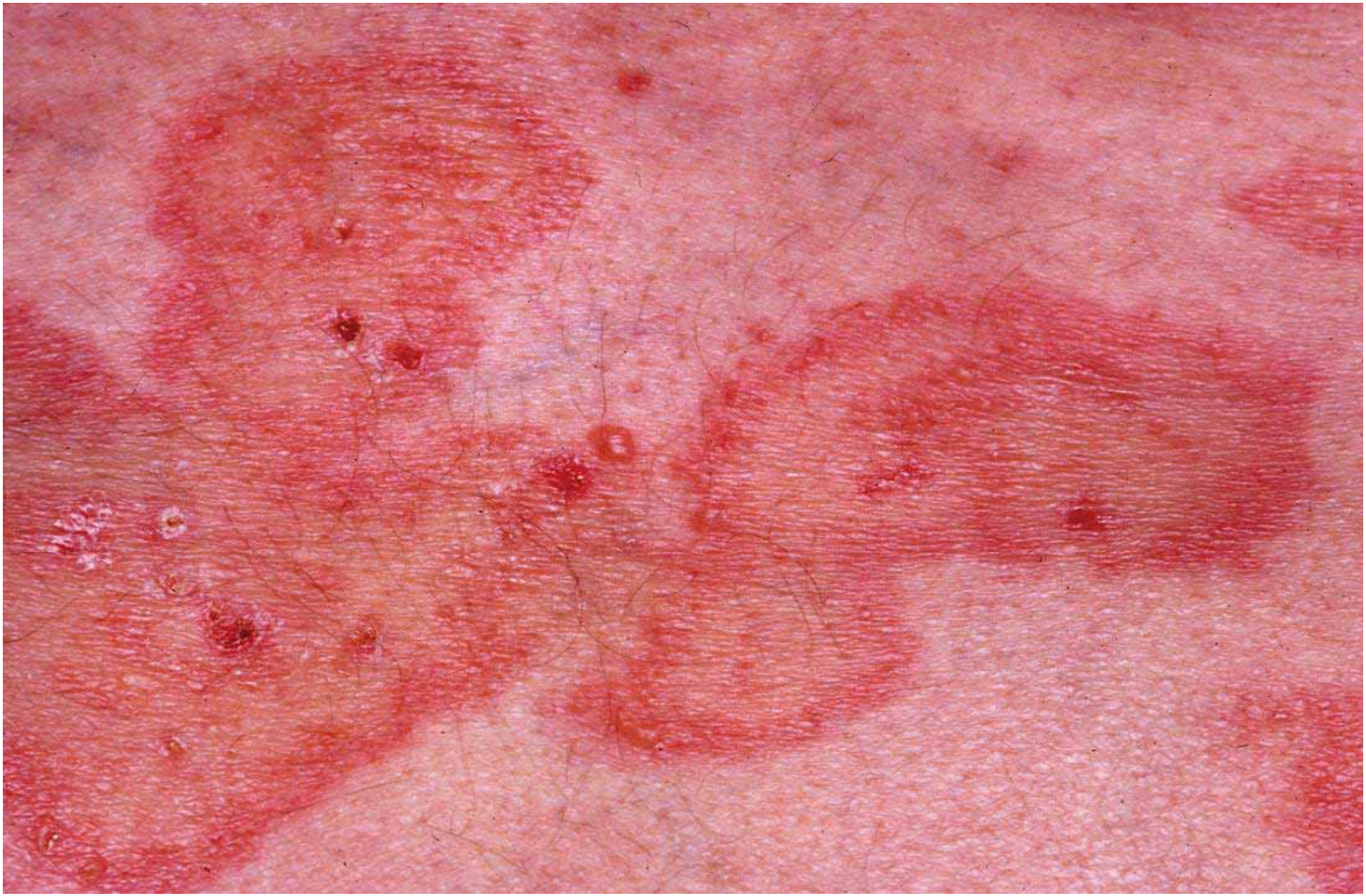
Eosinophil location	Clinical pattern	Disorder
Epidermis	Eczematous	Atopic dermatitis Contact dermatitis Cutaneous T cell lymphoma Hypereosinophilic syndrome with cutaneous manifestations Langerhans cell histiocytosis Scabies and larva migrans
Dermo-epidermal junction	Macular and papular	Drug eruption DRESS
Papillary dermis	Urticarial	Urticaria Eosinophilic cellulitis (Wells syndrome) Episodic angioedema with eosinophilia (Gleich syndrome) Polymorphic eruption of pregnancy
Subepidermal/papillary dermis and hair follicles	Blisters and pustules	Bullous pemphigoid Pemphigus Incontinentia pigmenti Eosinophilic pustular folliculitis Erythema toxicum neonatorum
Papillary and reticular dermis	Papular and nodular	Insect bite Prurigo nodularis Eosinophilic annular erythema Eosinophilic cellulitis (Wells syndrome) Angiolymphoid hyperplasia with eosinophilia and Kimura disease Eosinophilic dermatosis associated with hematologic malignancy Primary cutaneous CD30+ lymphoproliferative disorders
Subcutis	Panniculitic	Erythema nodosum Parasitic panniculitis
Superficial vascular dermal plexus	Vasculitic	Eosinophilic vasculitis Granuloma faciale Eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease)
Fascia	Fibrosis and sclerosis	Localized scleroderma Systemic sclerosis Eosinophilic fasciitis

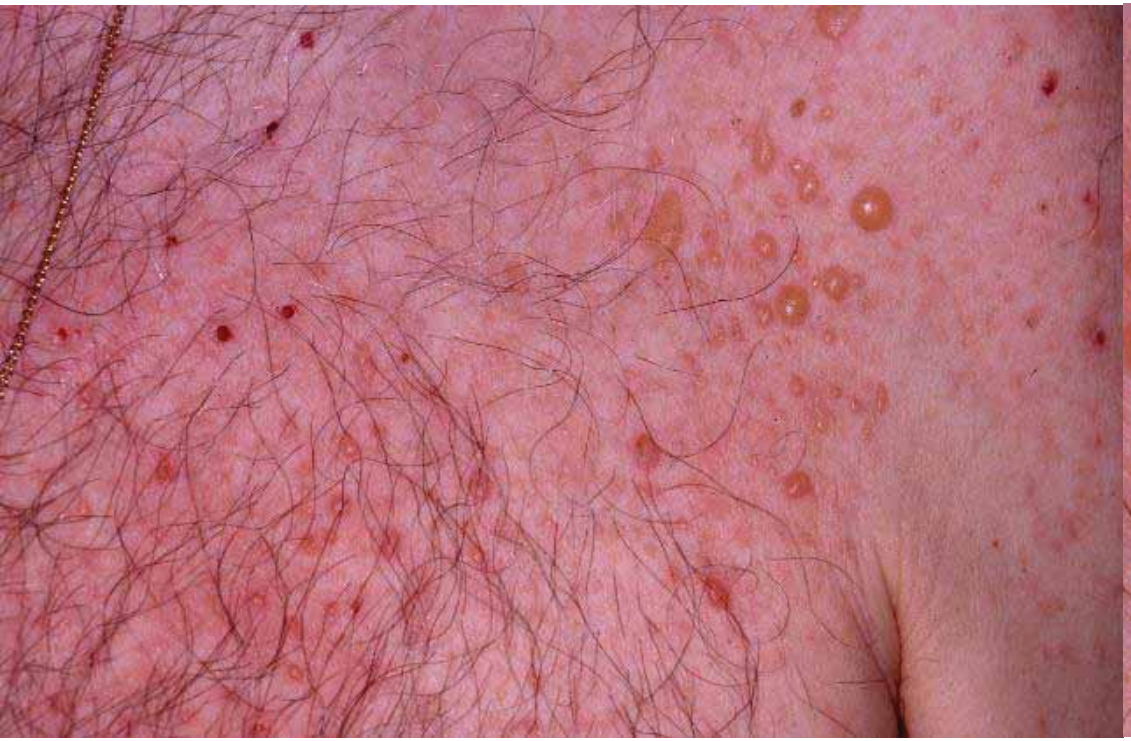
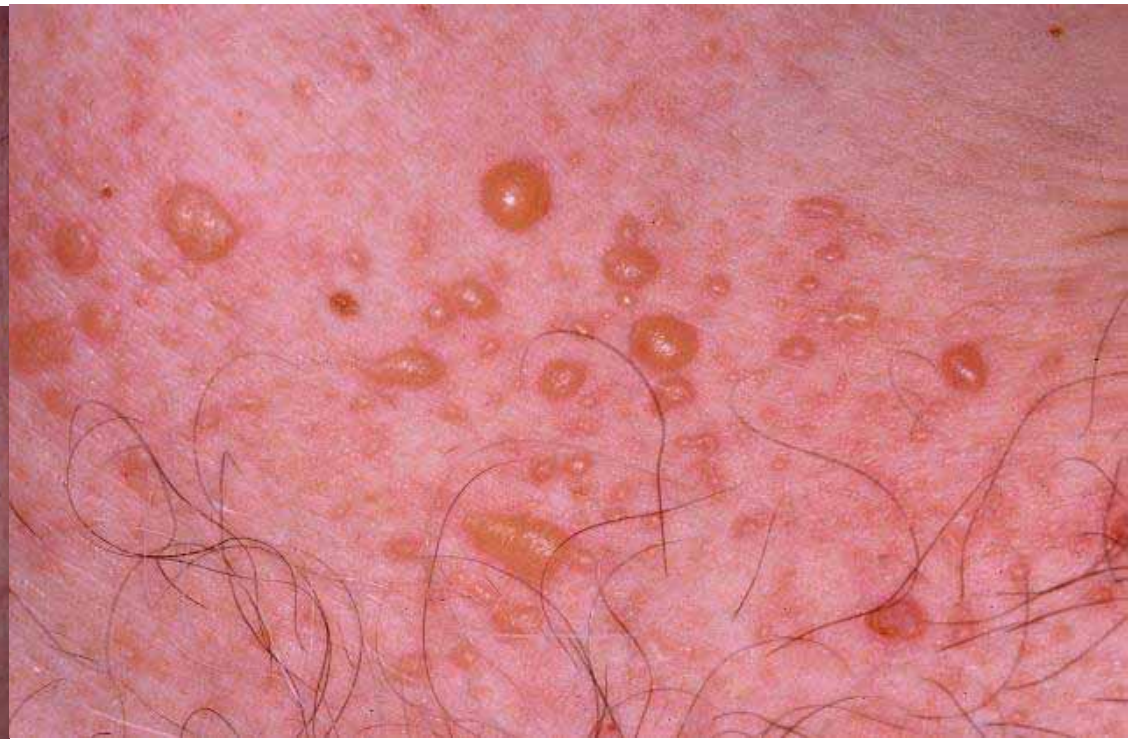
Pemphigus herpetiformis

Clinical features

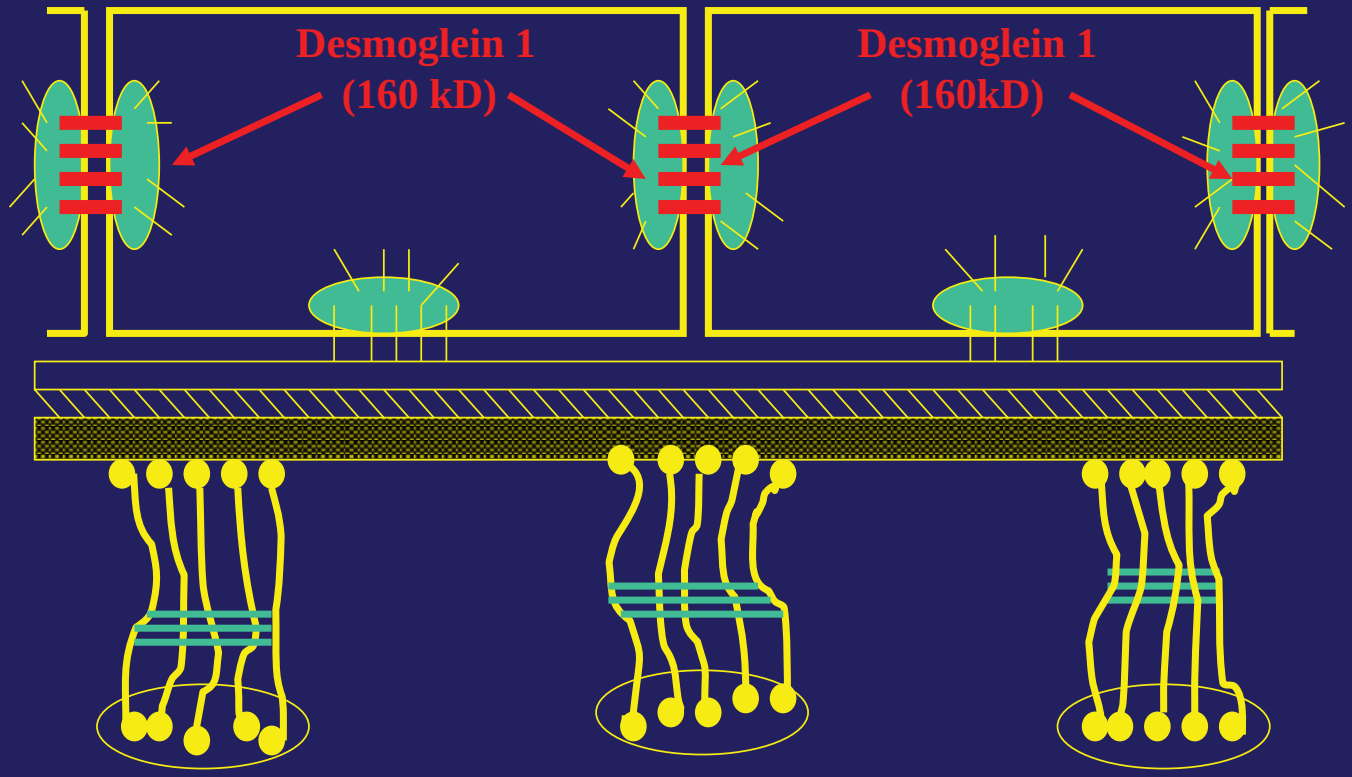
- A clinical variant of superficial pemphigus characterized by erythematous, pruriginous vesicular lesions mimicking dermatitis herpetiformis.
- Herpetiform arrangement of the lesions.
- Sometimes mucosal involvement.





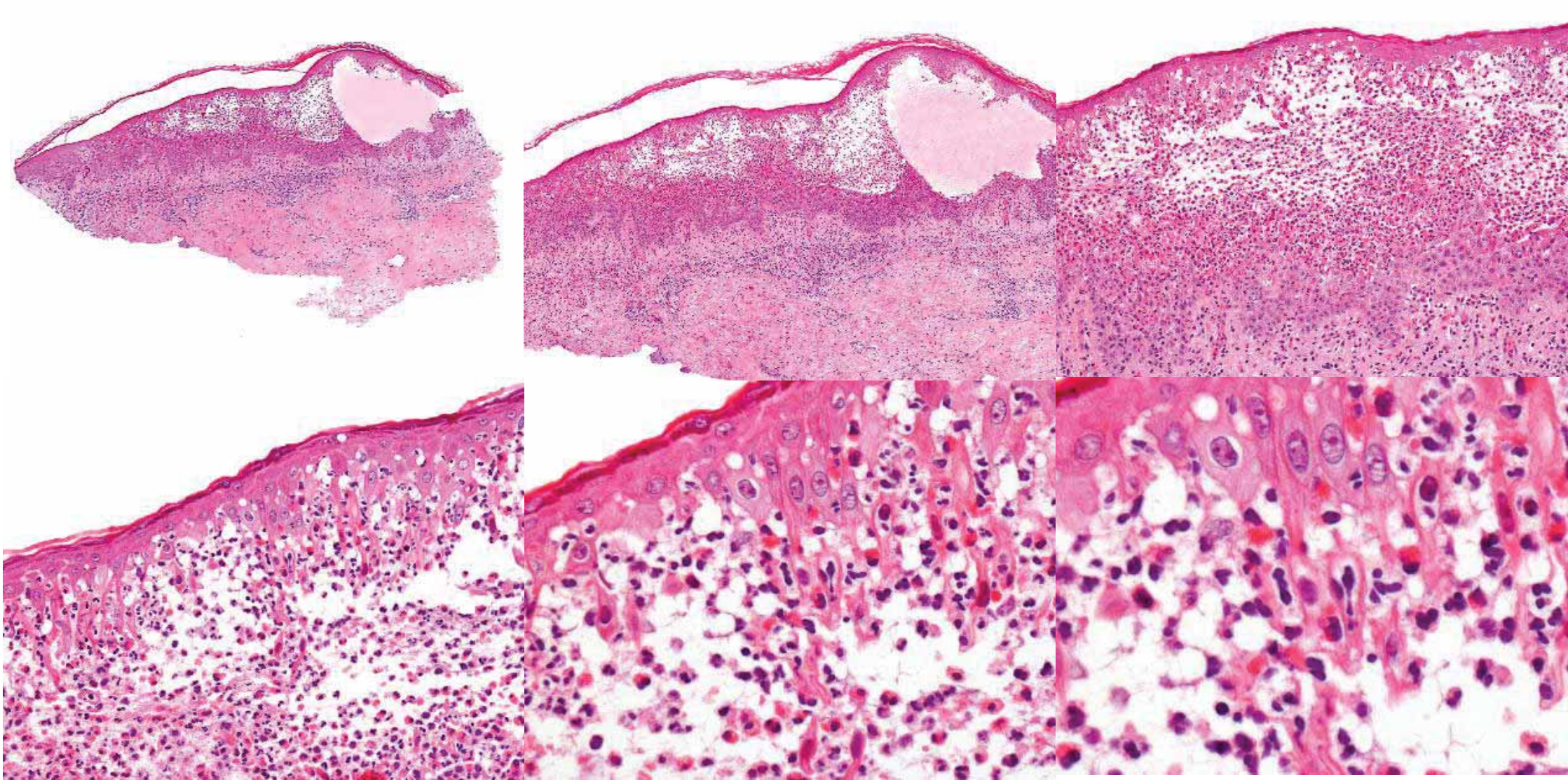
PEMPHIGUS HERPETIFORMIS

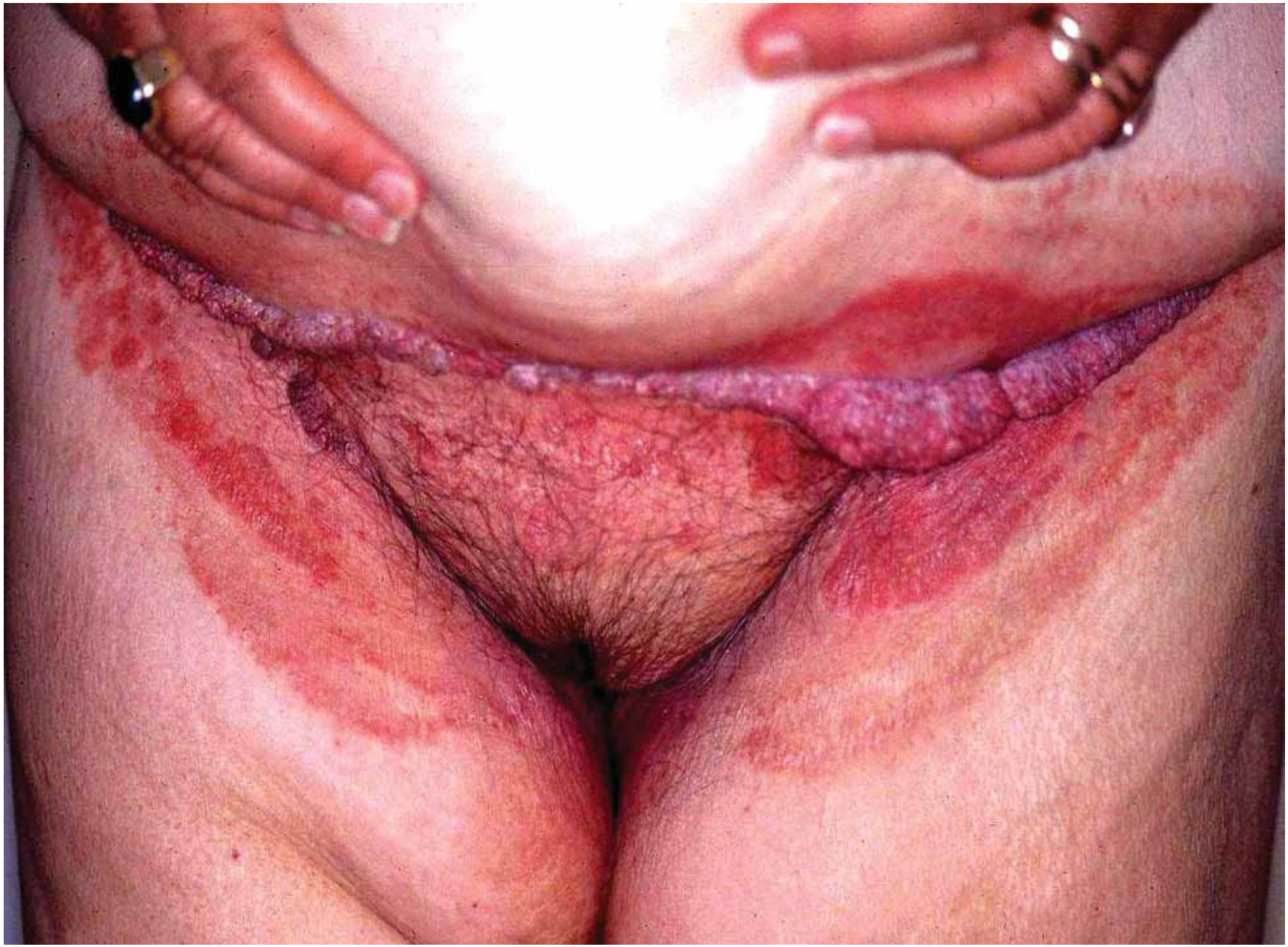


Pemphigus herpetiformis

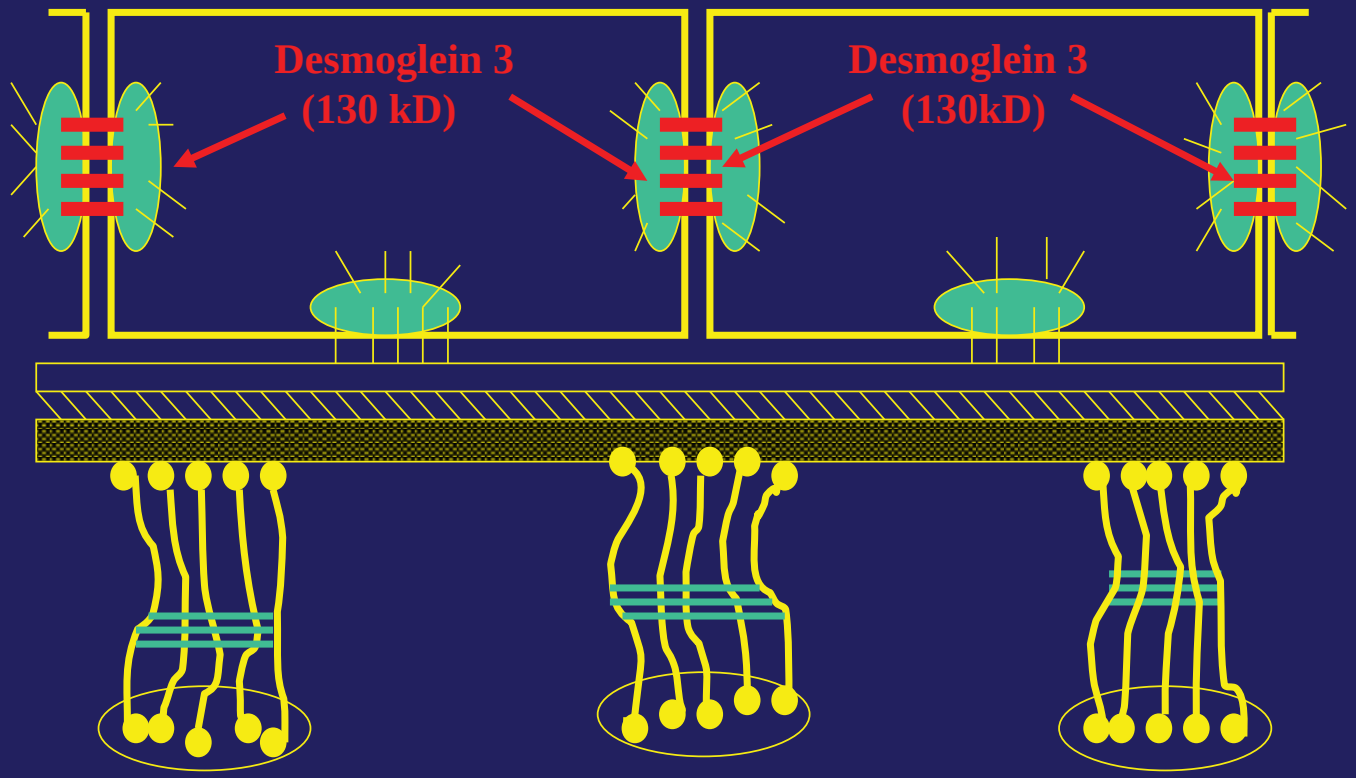
Histopathologic features

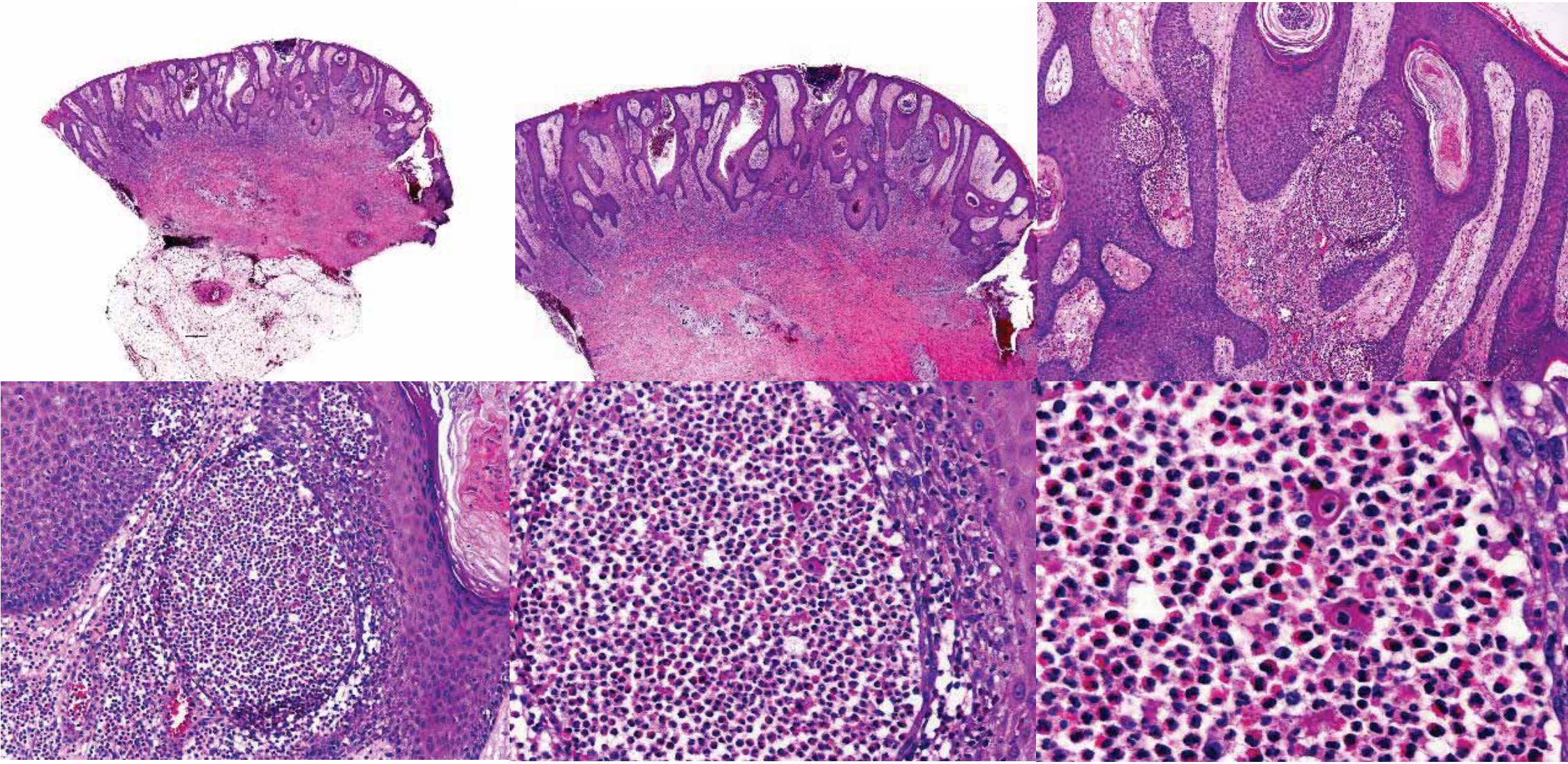
- Eosinophilic spongiosis with little or no acantholysis.
- Intraepidermal pustules with neutrophils and eosinophils.
- DIF: intercellular deposits of IgG in the upper half of the epidermis.
- Immunoblotting: desmoglein 1 and, less frequently, desmoglein 3.

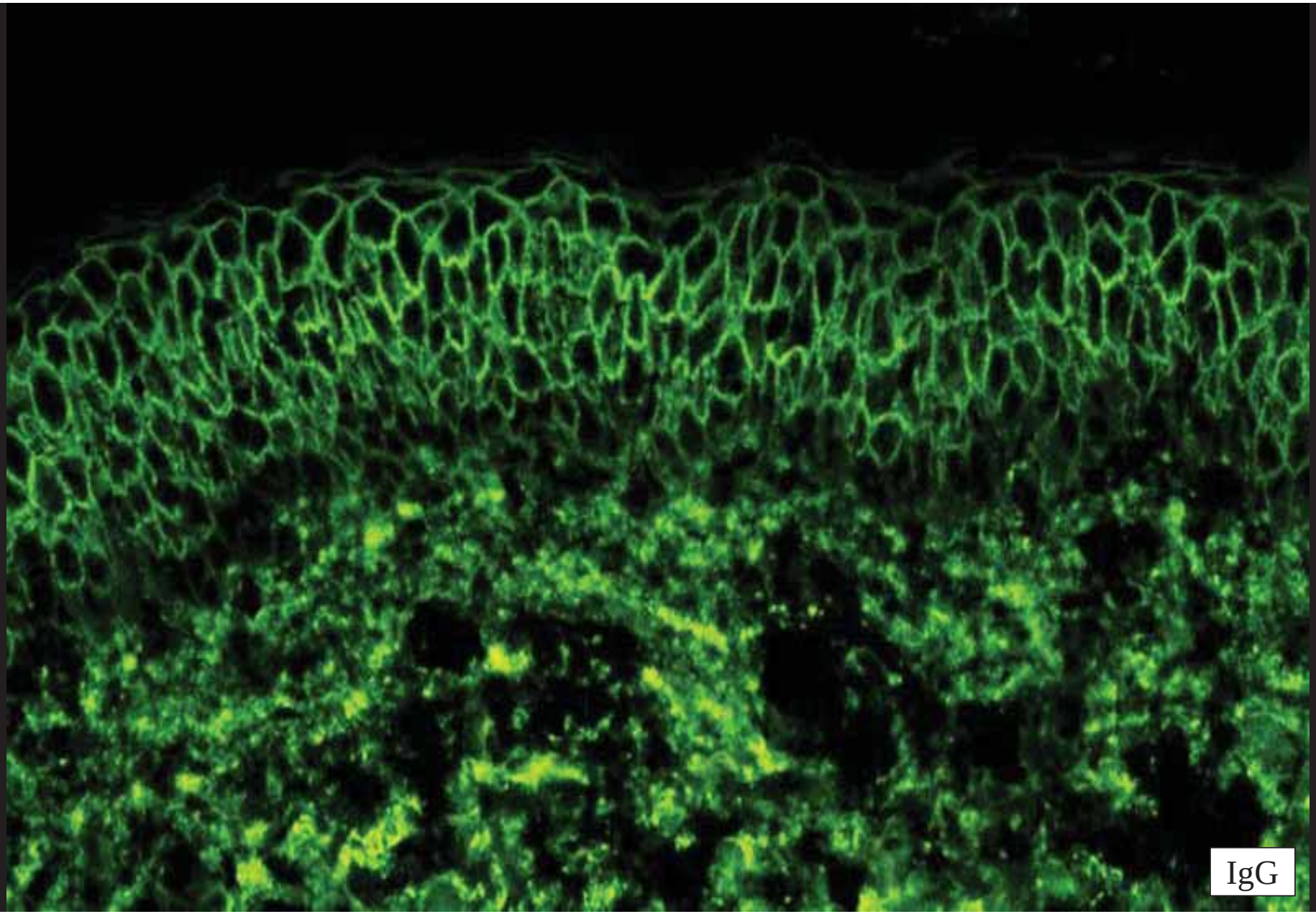




PEMPHIGUS VEGETANS






IgG

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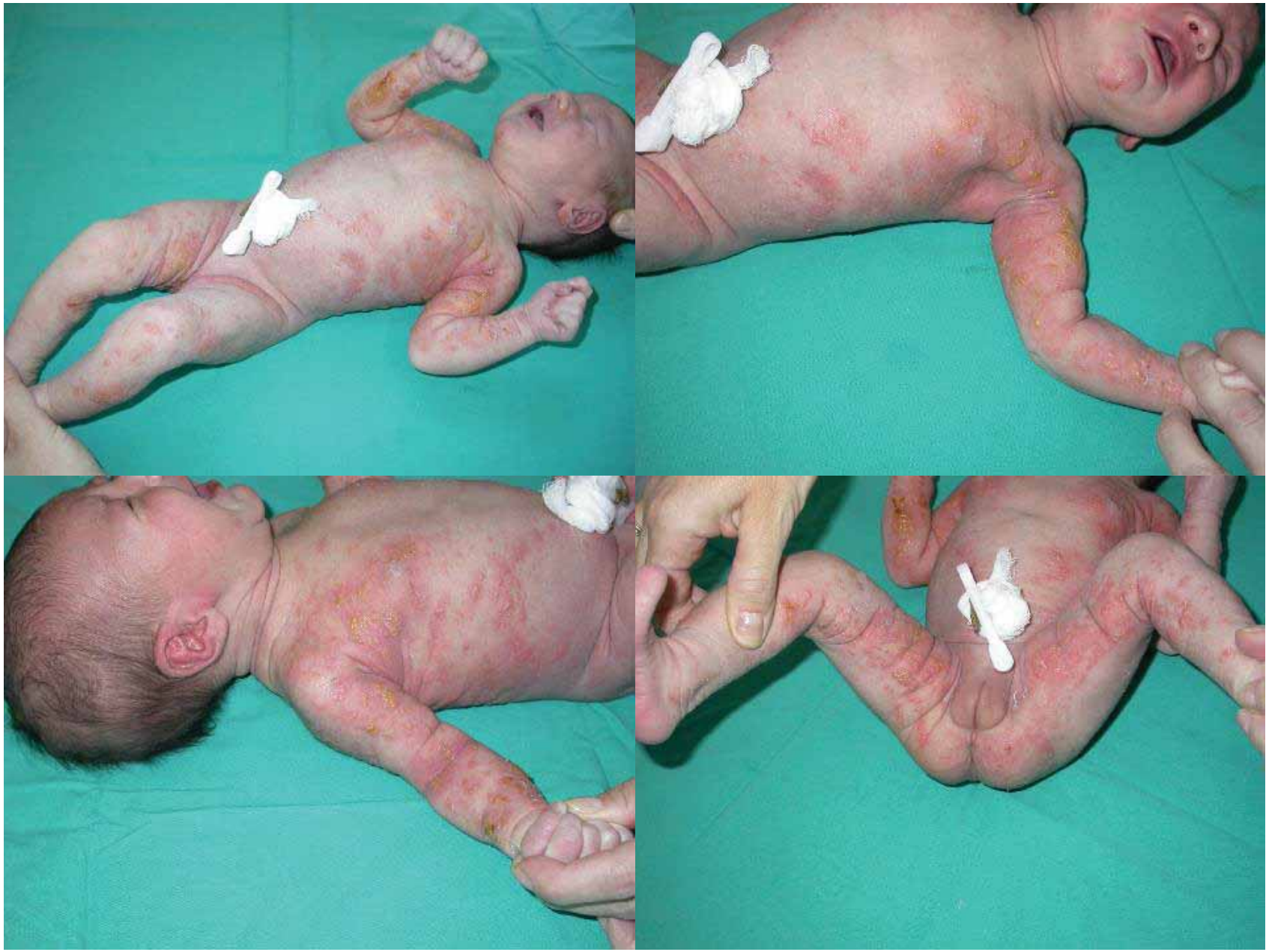
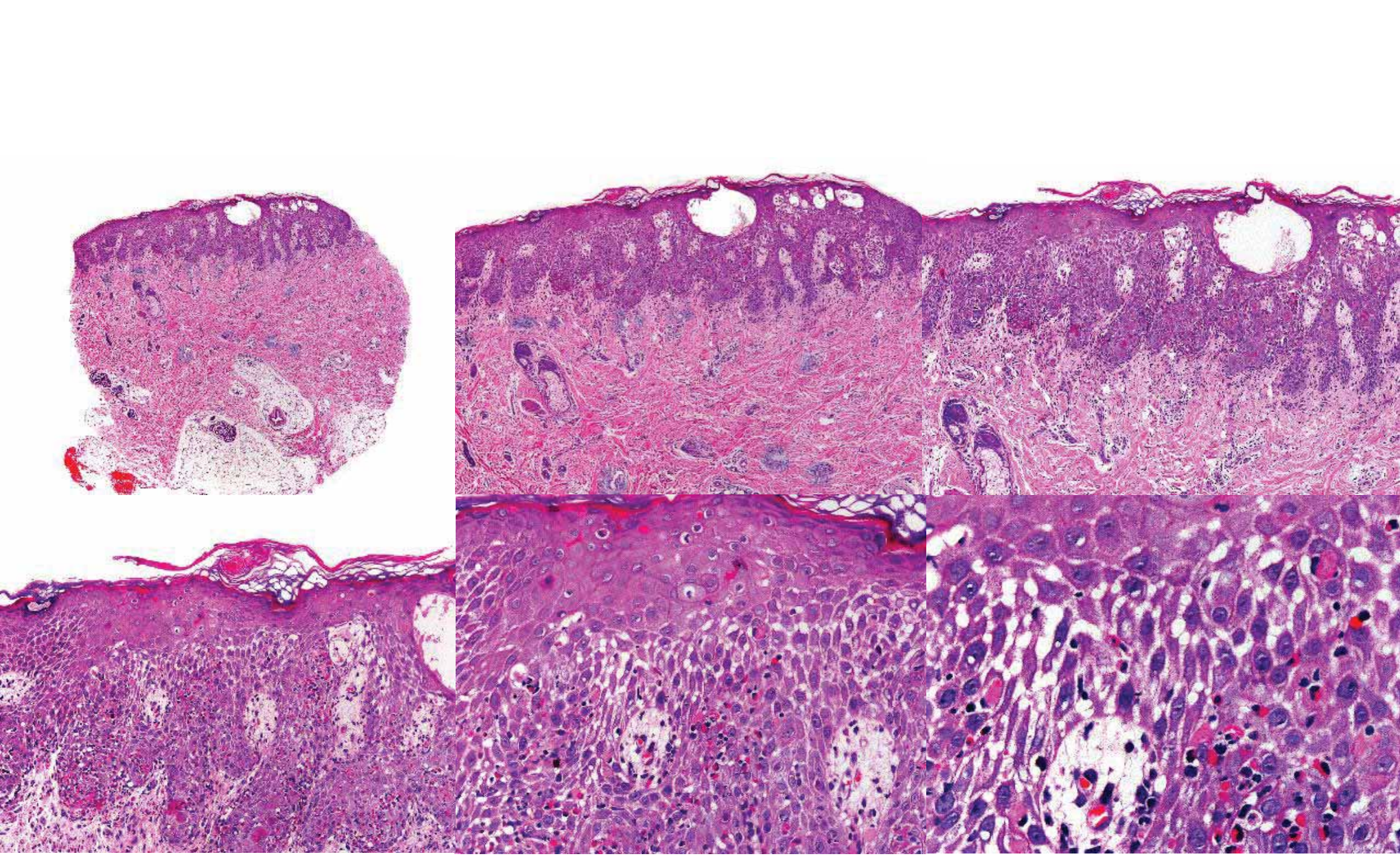
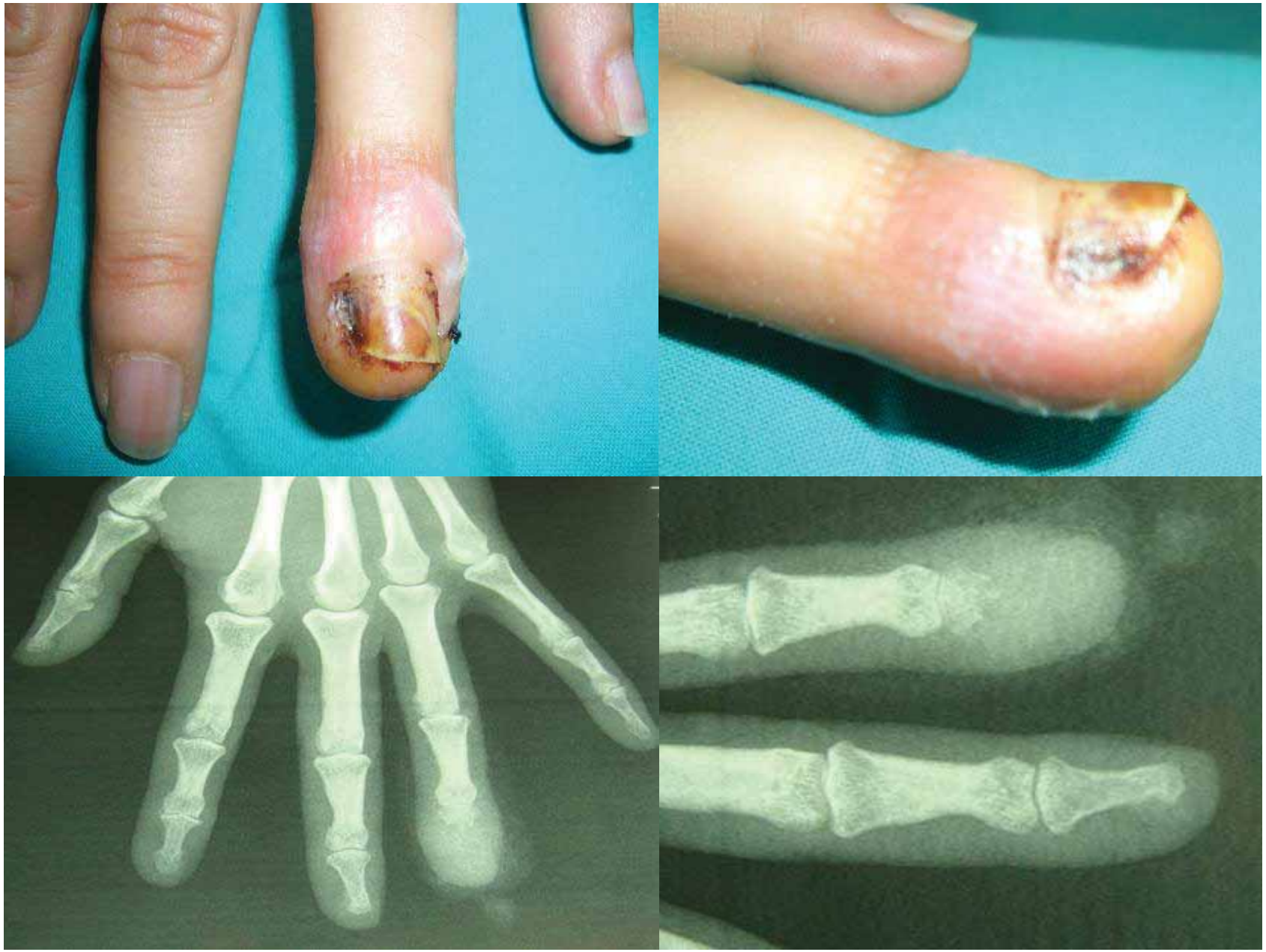
Fascia	Fibrosis and sclerosis	Localized scleroderma Systemic sclerosis Eosinophilic fasciitis

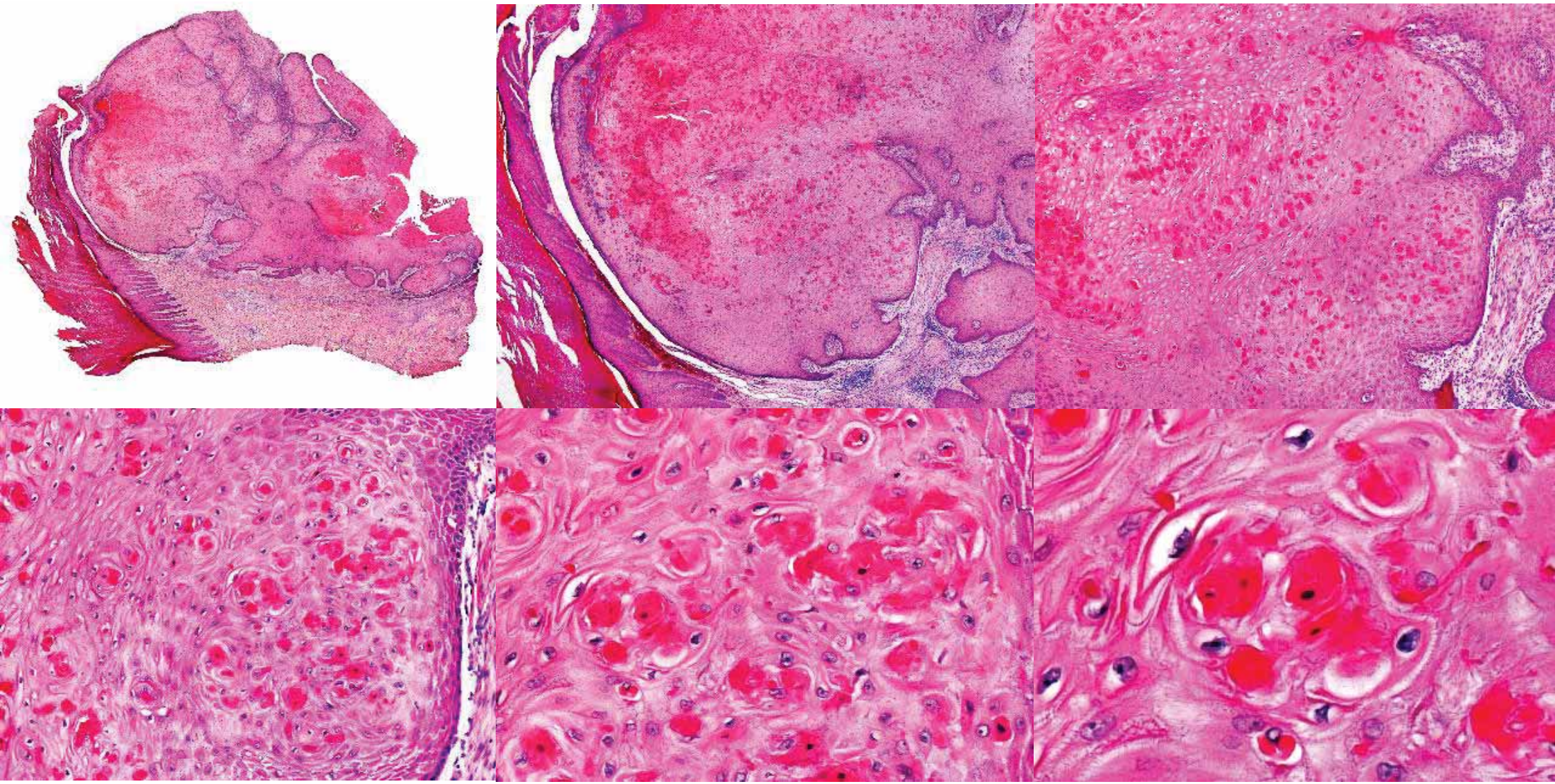
INCONTINENTIA PIGMENTI

- Genodermatosis with polydysplasia of ectodermal and mesodermal structures.
- X-linked dominant disorder due to mutations in the inhibitor of NF-kB kinase regulatory subunit γ (*IKBKG*), also known as *NEMO* gene.
- Lethal in male fetuses.
- Neurologic, ocular, dental and cutaneous lesions.
- Cutaneous lesions evolve through four classic phases: 1ª. Vesicular lesions in linear distribution; 2ª. Verrucous lesions; 3ª. Linear hyperpigmented lesions; and 4ª. Atropic hypopigmented streaks favoring the calves.
- Frequently, hyperkeratotic painful subungual lesions.









Painful subungual keratotic tumors in incontinentia pigmenti

José M. Mascaro, M.D., M.S., José Palou, M.D., and Pedro Vives, M.D.
Barcelona, Spain

We report a case of dyskeratotic subungual tumor in a 28-year-old woman. The patient presented achromic lineal lesions, typical of residual incontinentia pigmenti (IP), on her legs. Furthermore, the physical examination showed anodontia of the right incisor tooth. The familial background demonstrated miscarriages of male fetuses and characteristic dental abnormalities of IP in female siblings. The patient's daughter presented a typical background of IP and dyschromic splashed lesions. Light and electron microscopic studies of the subungual tumors were made. The analogy between subungual tumors of IP and keratoacanthoma is emphasized. (J AM ACAD DERMATOL 13:913-918, 1985.)

Incontinentia pigmenti (IP) is a hereditary X-linked complex process with peculiar cutaneous manifestations described by Bloch[1] in 1926 and by Sulzberger[2] in 1928. The cutaneous features evolve classically in three stages: (1) in the first stage, which is usually present at birth, there is a linear erythematovesicular and bullous eruption; (2) in the second, verrucous lesions appear; and (3) finally, the third stage is characterized by a splashed or whorled pigmentation. It is well known that multiple ectodermal and mesodermal defects occur in IP: about 79.8% of all patients with IP appear to have one or more abnormalities of hair, nail, eyes, teeth, central nervous system, and structural development.[3]

Review of the literature reveals only two previous reports of painful subungual tumors associated with this disease.[4] This article reports a new case.

CASE REPORT

A 28-year-old woman was admitted to our department of dermatology for diagnosis and treatment of painful tumors on the first and fifth fingers of the right hand and on the fourth finger of the left hand.

At approximately 23 years of age the patient began to develop nail changes and painful subungual tumors of the first and second fingers of right hand. The first symptoms began in August, 1979, with pinprick sensations on the tips of the affected fingers. The region became swollen, erythematous, and extremely painful, even when only slightly traumatized. The patient had been examined in another department, where radiography, angiography, and cultures for bacteria and fungi were carried out. All results were negative except for the radiological examination, which demonstrated osteolytic lesions of the distal phalanges of the first finger (Fig. 1). In December, 1979, the lesions were surgically removed without a definite diagnosis. The patient remained asymptomatic during 4 years. In July, 1983, new lesions appeared on the fourth and fifth fingers of the left hand, with identical clinical manifestations.

The patient showed nail dystrophy of the affected fingers, closely related to raised painful tumors that appeared as keratotic masses extending from beneath the nail, giving the whole distal phalanges a swollen appearance (Figs. 2 to 4). The clinical aspect of these lesions, similar to those in the previous cases seen in our department 12 years before, led us to carry out a more complete physical examination. This examination revealed achromic and atrophic lineal and reticular lesions on the inner region of her thighs and legs. Furthermore, anodontia of the right upper incisor was

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"Perhaps we could consider that the lesions that appear in patients affected by IP are subungual keratoacanthoma, because the clinical and histologic aspects of both entities, as well as their evolution, are indistinguishable."

EOSINOPHILIC DERMATOSES

Eosinophil location	Clinical pattern	Disorder
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Acta Dermatovener (Stockholm) 50, 195–203, 1970

EOSINOPHILIC PUSTULAR FOLLICULITIS

Shigeo Ofuji, Atsuhiko Ogino, Takeshi Horio, Takeji Ohseko and Masami Uehara

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Abstract. The main feature of the cases presented here is the repeated appearance of crops of pruritic follicular sterile papulopustules in fairly well defined areas of the face, trunk and extremities, and not on the hands and feet. They extended centrifugally, i.e., fresh eruptions appeared at the periphery as old ones faded in the center. When plaques reached a certain size, they subsided leaving pigmentation. Histologic examination revealed vesicles in the outer root sheath containing many eosinophils and extending from the subcorneal portion of the follicular ostium to the level of the entry of the sebaceous gland, occasionally reaching the gland itself. These clinical and histologic features do not correspond with any of the known dermatoses, and the name "eosinophilic pustular folliculitis" is proposed.

Folliculitis with pustulation occurs not only in infectious diseases, but also in sterile conditions, such as contact dermatitis, autosensitization dermatitis, trichophytids, drug eruptions and erythema toxicum neonatorum. The authors have recently treated three cases with peculiar clinical and histologic features of folliculitis with sterile pustulation, and hereby propose a new name "Eosinophilic pustular folliculitis" for this condition. This paper reports these three cases and re-evaluates a similar case reported previously.

CASE REPORTS

Case 1

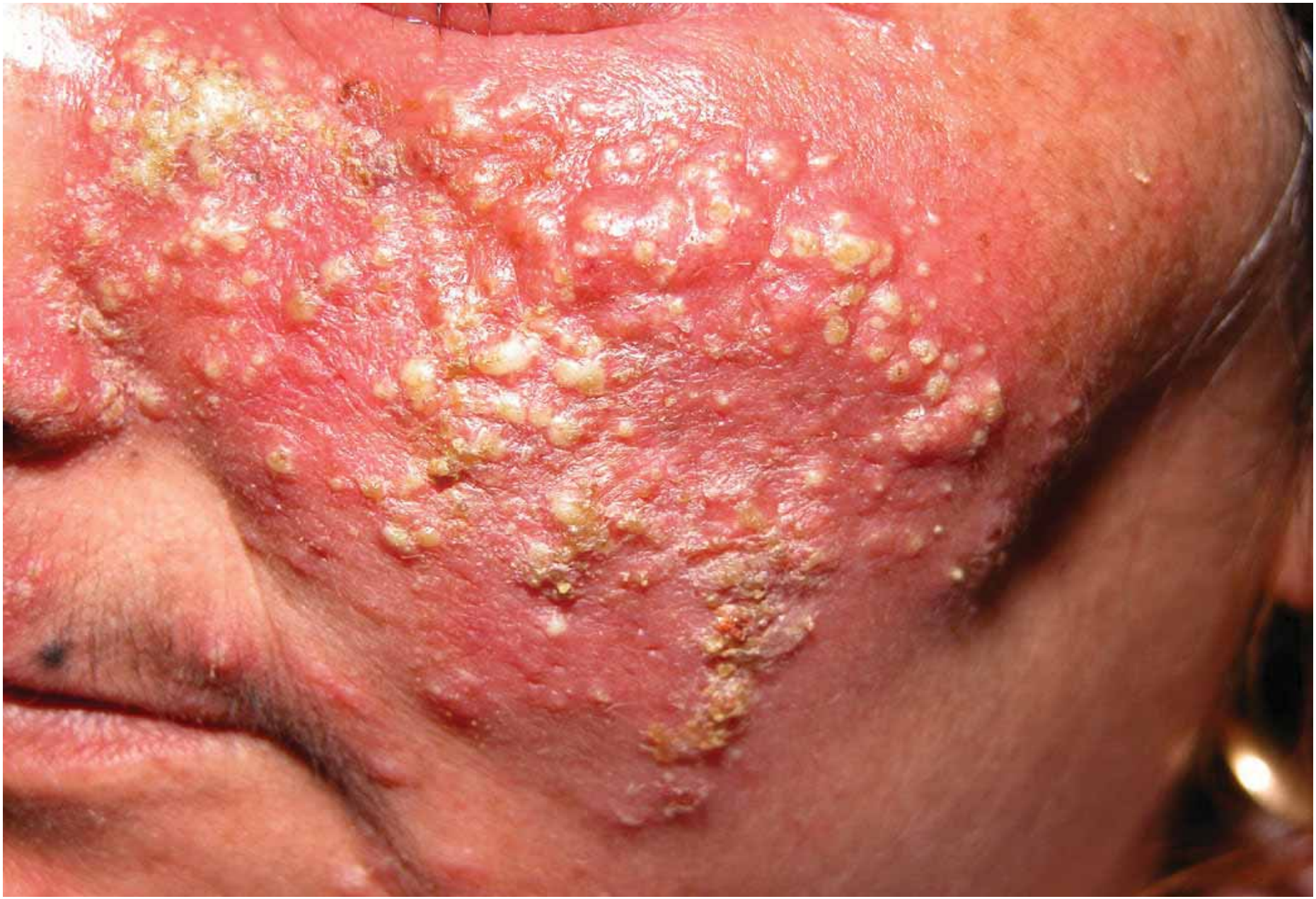
A 27-year-old Japanese carpenter was first seen at the Kyoto University Hospital on November 4, 1966. He first noticed a pruritic plaque consisting of papules and pustules on the extensor surface of the left upper arm in January, 1964. As the lesion gradually grew to about 10 cm in diameter, new papules and pustules developed principally at the periphery while those in the central area subsided. Later, similar lesions developed successively on the right upper arm, chest, back and face. These underwent remissions and exacerbations but caused no general symptoms except for slight malaise at the beginning of the more severe exacerbations. He had had tinea pedis for over ten years. His father had bronchial asthma.

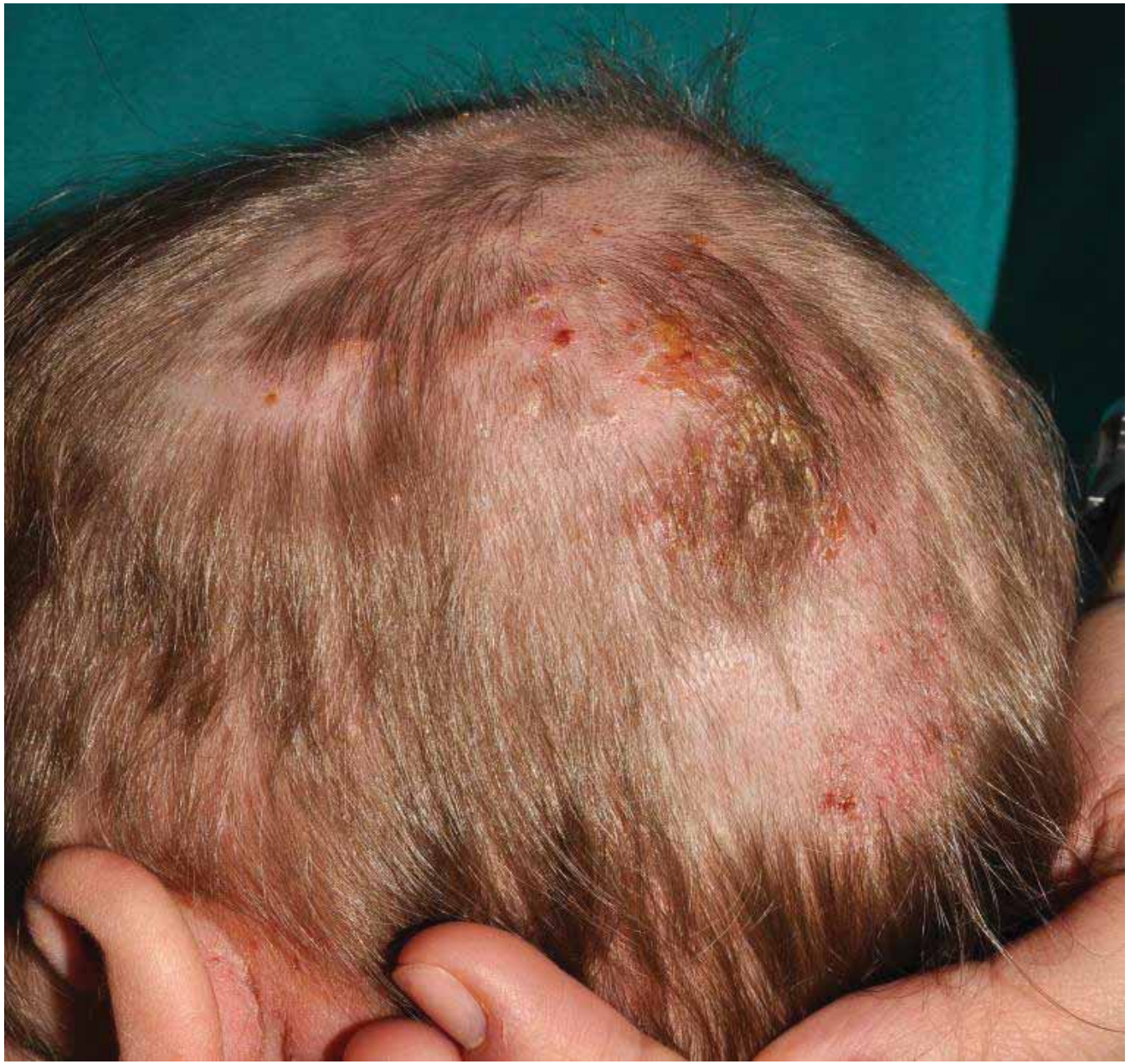
Clinical findings. The patient was a healthy-looking young man with seborrheic facial skin. A few folliculitides along with comedones from acne vulgaris were present on the face, chest and back. The skin lesions in question covered almost entirely the face, chest, back and extensor surfaces of the upper arms except for the orbital region, lower lip, anterior surface of the neck, nape and axillae (Fig. 1). The scalp was covered with pityriatic scales. Patchy lesions were noted on the abdomen and over the sacrum. Each lesion consisted of numerous follicular papules in an area of diffuse brownish pigmentation. The fresh active eruptions were red papules 1 to 2 mm in diameter surrounded by a red halo and topped with a pustule (Fig. 2). These papulopustules were observed chiefly at the periphery of the lesions while, in the pigmented center, reddish brown papules with some scales were seen; this appeared to be a fading process (Fig. 3). Hairs were present in many papulopustules. The involved areas were redder and less pigmented on the face than in other areas. Follicular papulopustules were scattered over the extensor surfaces of the thighs. The mucous membranes were not involved. Physical examination revealed no other abnormalities except for chronic tonsillitis.

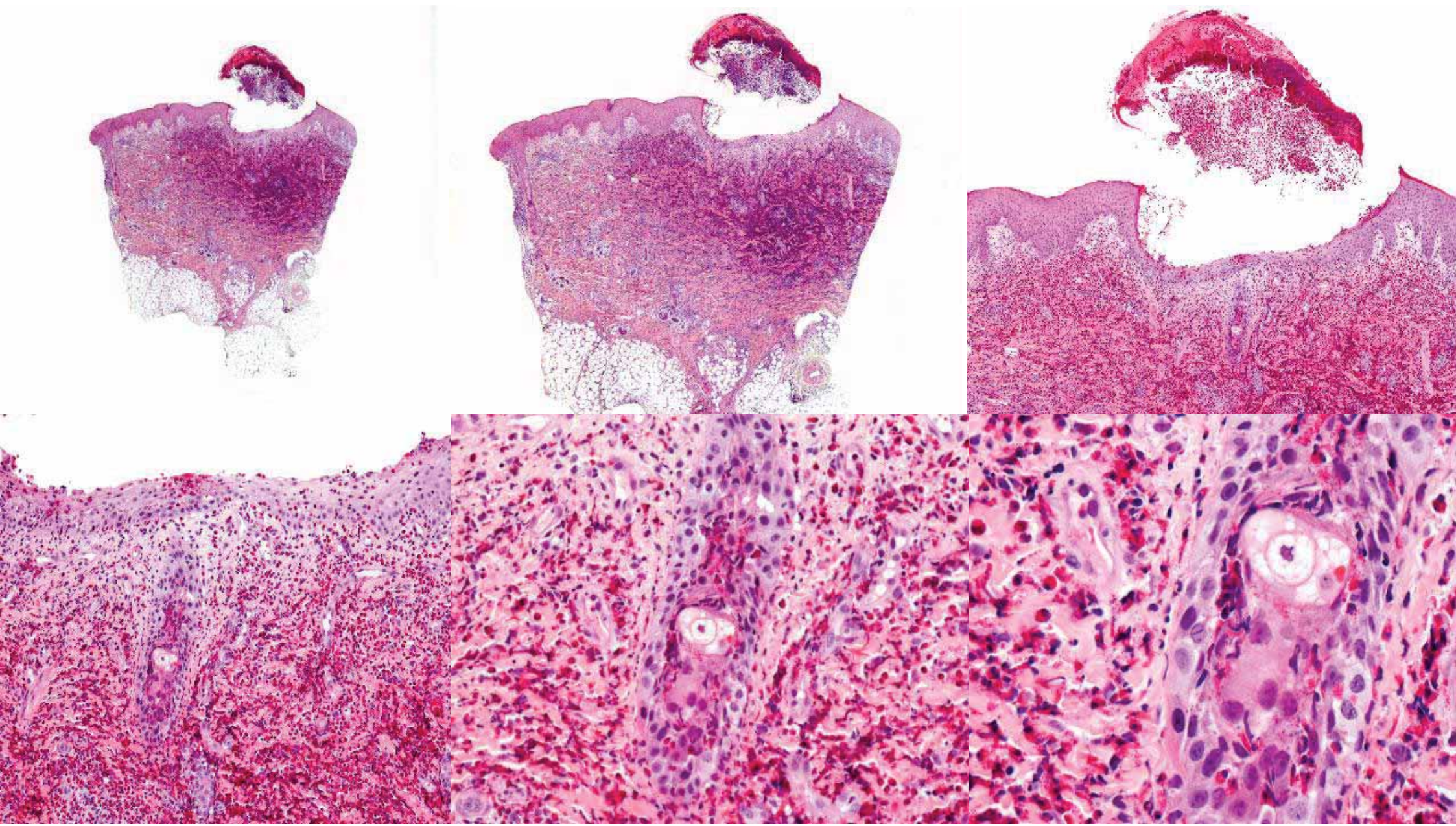
Laboratory findings. The blood count on admission revealed WBC 18,800 with a differential count of 39% neutrophils, 41% eosinophils, 1% basophils, 4% monocytes and 15% lymphocytes. During the following 3 months, under various treatments, the WBC ranged from 7200 to 10,600 and the eosinophils from 7 to 46%. Other laboratory studies including liver function tests, sedimentation rate, serum protein electrophoresis, C-reactive protein, ASLO and RAT were within normal limits. Serologic reaction for syphilis was negative. Stools were free of ova and parasites. Mycelial elements were negative for microscopic examination. Bacterial cultures from the pustules repeated three times in fluid thioglycolate medium, heart infusion agar and blood agar, did not show any growth. Both immediate and delayed reactions were negative to intradermal tests of the following agents: trichophytin, vaccines of staphylococcus aureus, streptococcus hemolyticus and corynebacterium acnes. Smears from the pustules showed eosinophils, most of which

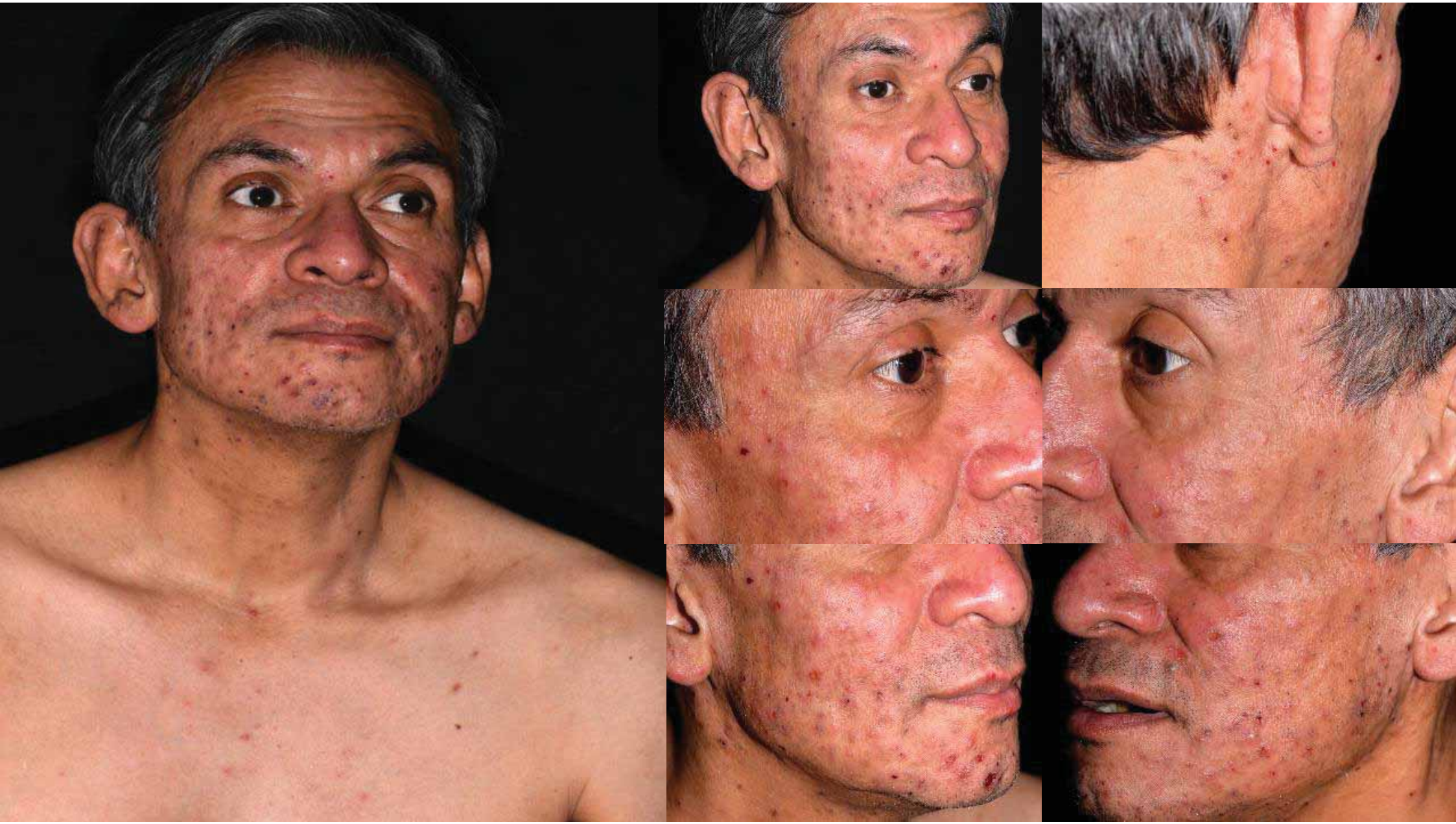
EOSINOPHILIC PUSTULAR FOLLICULITIS

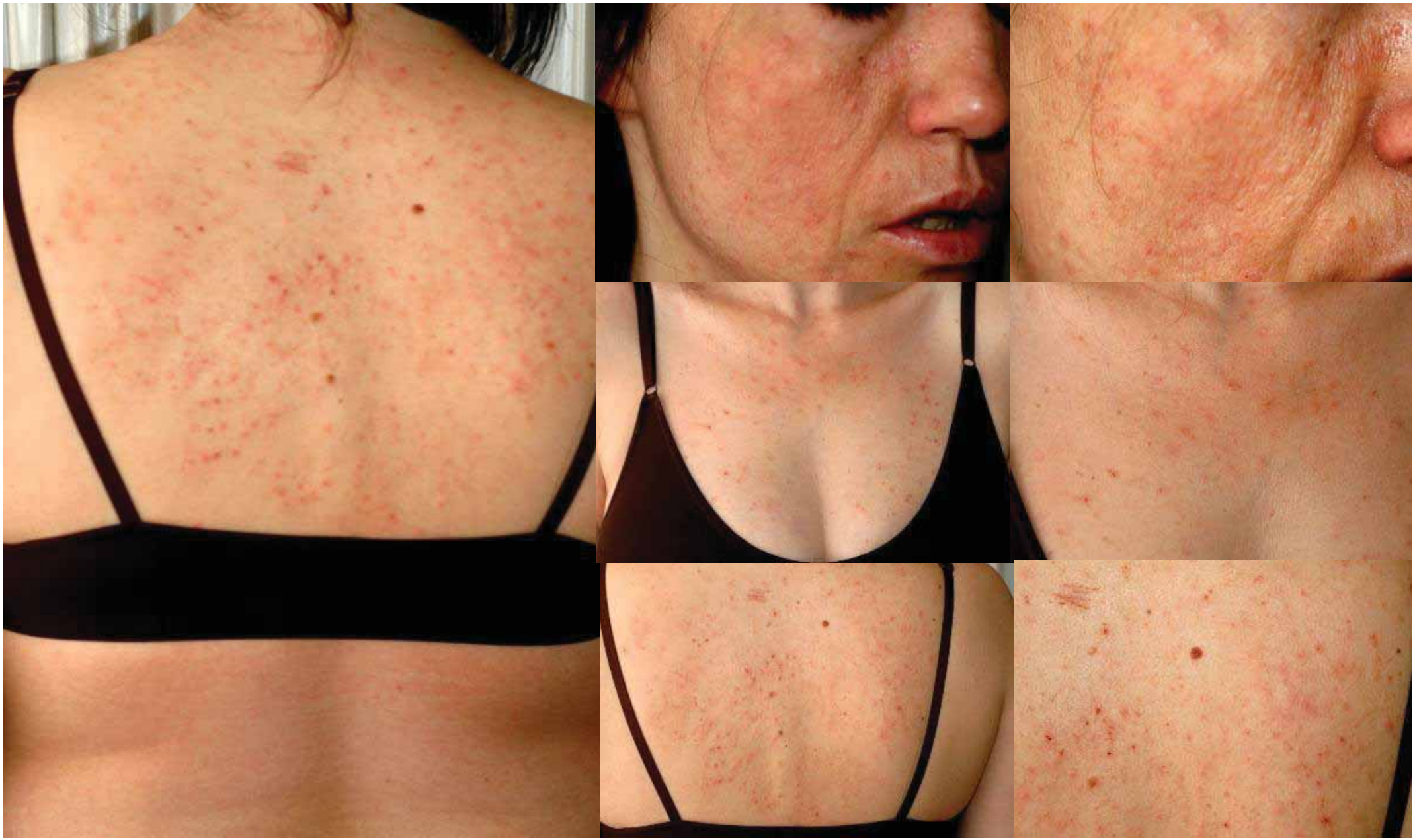
- **Classic type (Ofuji disease)**: chronic recurrent clusters of pruritic sterile follicular pustules arranged in annular plaques with central clearing and centrifugal extension, most frequently on the face of adults.
- **Infantile type**: rare, mostly in infants less that one year of age. Reccurrent pruginous pustules mostly on the scalp. In most cases the disease resolves spontaneously in 2-3 years.
- **Immunosuppression-associated type**: mainly associated with HIV infection and hematological malignancies. Erythematous and pruriginous follicular papules and pustules on the face, upper trunk and upper extremities.

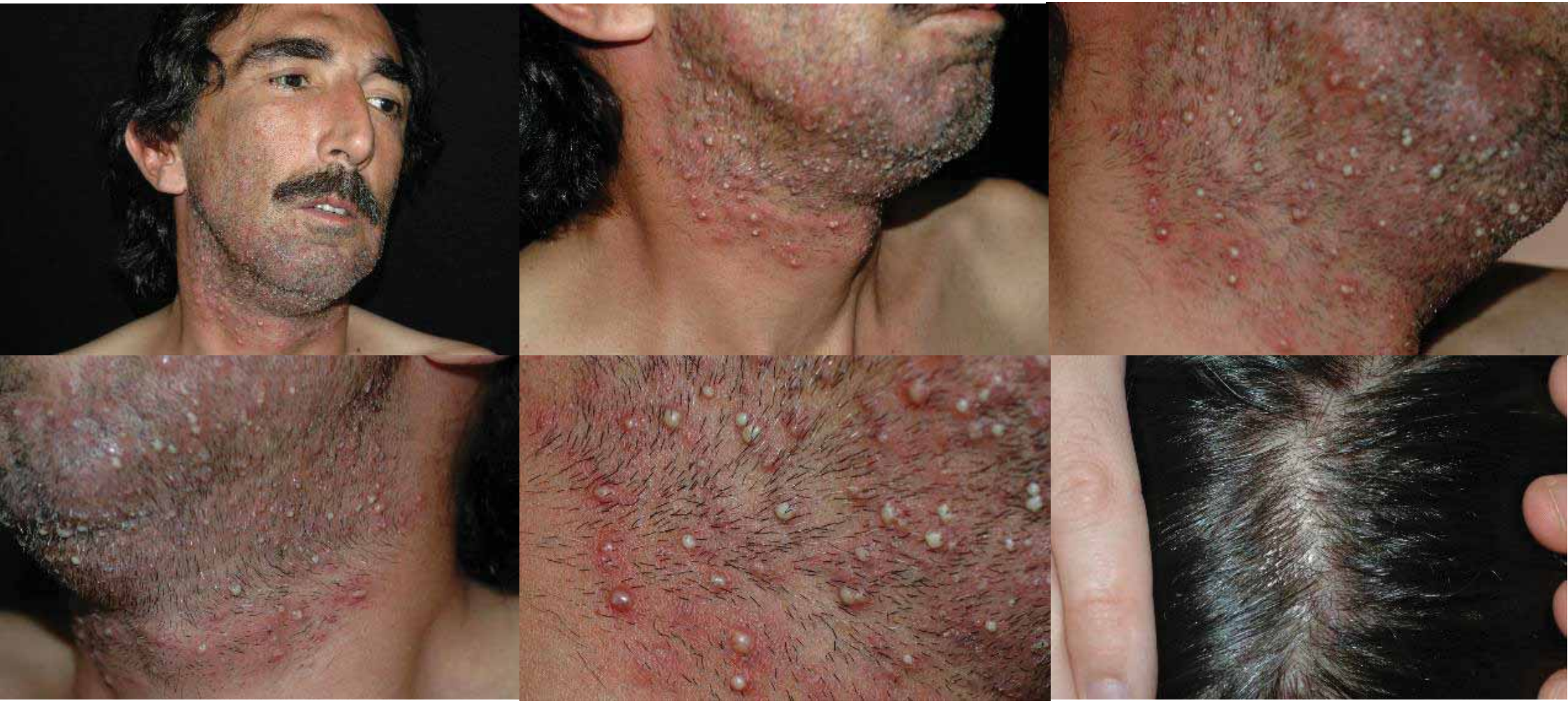












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Foliculitis por *candida albicans* en drogadicto intravenoso

Folliculitis due to candida albicans in an intravenous drug-abuser

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Resumen
La foliculitis candidiásica es casi exclusiva de los consumidores de heroína marrón por vía intravenosa. Es debida a una infección sistémica por *Candida albicans*.
Describimos el caso de un varón de 42 años de edad, VIH negativo, adicto a drogas por vía parenteral, que consultó por la presencia de pápulas y pústulas foliculares dolorosas localizadas en regiones pilosas, la barba, el cuero cabelludo, zona centrotorácica y genital, de 48 horas de evolución, junto a fiebre, malestar general y artromialgias desde hacía una semana. En el estudio oftalmológico se demostró la existencia de retinitis bilateral candidiásica junto a uveítis anterior aguda en el ojo izquierdo. En el estudio histopatológico de las lesiones cutáneas se demostró la presencia de microabscesos foliculares, y un leve infiltrado inflamatorio perifolicular compuesto por linfocitos y polimorfonucleares. En el cultivo de las lesiones cutáneas en medio Sabouraud, se aisló *Candida albicans*.
En la década de los noventa la incidencia de la candidiasis sistémica en drogadictos intravenosos disminuyó notablemente, siendo en la actualidad una entidad excepcional que aún hoy, hay que tener presente.

(E. González-Guerra, R. Haro, MªC Fariña, L. Martín, L. Requena. Foliculitis por candida albicans en drogadicto intravenoso. Med Cutan Iber Lat Am 2009;37(4):188-191)

Palabras clave: foliculitis candidiásica, candidiasis diseminada, heroína marrón.

Summary
Candidiasic folliculitis is almost exclusive disease of intravenous brown heroin abusers. It is ambiguous due to a systemic infection by Candida albicans. A 42 year-old man, HIV negative and intravenous drug abuser, who was referred with painful follicular papules and pustules located on hairy regions of the beard, scalp, thoracic and genital areas is reported. The patient had also fever, general discomfort and artromyalgias. The ophthalmologic examination demonstrated bilateral candidiasic retinitis and left acute anterior uveitis. Histopathological study showed follicular microabscesses and slight inflammatory infiltrate with perifollicular arrangement and composed of lymphocytes and neutrophils. Culture of the biopsy specimen isolated Candida albicans.
In the decade of the nineties the incidence of the systemic candidiasis, diminished notably, being at present an exceptional entity although it is necessary to be aware the process.

***Key words:** candidiasic folliculitis, systemic candidiasis, brown heroin.*

En 1980 se introdujo en Europa una heroína importada de Irán en forma de pasta húmeda, que necesita ácido cítrico para su disolución, denominada heroína marrón por su aspecto. Parece ser que sobre la pasta húmeda de esta heroína marrón, la *Candida albicans* se desarrolla con facilidad. Un año después se publicaron en París los primeros casos de candidiasis sistémica en heroinómanos. En 1983 se describen las manifestaciones cutáneas, oculares y osteoarticulares de la enfermedad en este grupo de pacientes, considerándola como un nuevo síndrome diferente de las candidiasis sistémicas de pacientes inmunodeprimidos o de pacientes postoperatorios[1, 2]. En España, el uso de la heroína marrón estaba muy extendido en la década de los 80 y el primer caso clínico fue descrito en 1983 por Guerra et

PGD_2 induces eotaxin-3 via PPARγ from sebocytes: A possible pathogenesis of eosinophilic pustular folliculitis

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Background: Eosinophilic pustular folliculitis (EPF) is a chronic intractable pruritic dermatosis characterized by massive eosinophil infiltrates involving the pilosebaceous units. Recently, EPF has been regarded as an important clinical marker of HIV infection, and its prevalence is increasing in number. The precise mechanism by which eosinophils infiltrate into the pilosebaceous units remains largely unknown. Given that indomethacin, a COX inhibitor, can be successfully used to treat patients with EPF, we can assume that COX metabolites such as prostaglandins (PGs) are involved in the etiology of EPF.
Objective: To determine the involvement of PGs in the pathogenesis of EPF.
Methods: We performed immunostaining for PG synthases in EPF skin lesions. We examined the effect of PGD_2 on induction of eotaxin, a chemoattractant for eosinophils, in human keratinocytes, fibroblasts, and sebocytes and sought to identify its responsible receptor.
Results: Hematopoietic PGD synthase was detected mainly in infiltrating inflammatory cells in EPF lesions, implying that PGD_2 was produced in the lesions. In addition, PGD_2 and its immediate metabolite 15-deoxy-Δ 12,14-PGJ_2 (15d-PGJ_2) induced sebocytes to produce eotaxin-3 via peroxisome proliferator–activated receptor gamma. Consistent with the above findings, eotaxin-3 expression was immunohistochemically intensified in sebaceous glands of the EPF lesions.
Conclusion: The PGD_2/PGJ_2-peroxisome proliferator–activated receptor gamma pathway induces eotaxin production from sebocytes, which may explain the massive eosinophil infiltrates observed around pilosebaceous units in EPF. (J Allergy Clin Immunol 2012;129:536-43.)

Key words: Prostaglandin D_2, hematopoietic prostaglandin D synthase, eotaxin-3/CCL26, sebocyte, peroxisome proliferator–activated receptor gamma

Abbreviations used
- $CRTH_2$: Chemoattractant receptor–homologous molecule expressed on T_H2 cells
- EPF: Eosinophilic pustular folliculitis
- GAPDH: Glyceraldehyde 3-phosphate dehydrogenase
- H-PGDS: Hematopoietic prostaglandin D synthase
- L-PGDS: Lipocalin-type prostaglandin D synthase
- PG: Prostaglandin
- PPARγ: Peroxisome proliferator–activated receptor gamma
- siRNA: Small interfering RNA

Eosinophilic pustular folliculitis (EPF) is a chronic intractable pruritic dermatosis characterized by massive eosinophil infiltrates involving the pilosebaceous units.[1] The evidence accumulated to date indicates that T_H2-mediated immunologic mechanisms are involved in the pathogenesis of EPF.[2,3] Recently, EPF has been regarded as an important clinical marker of HIV infection, and its prevalence is increasing in number.[4] An immunohistochemical study has demonstrated the expression of intercellular adhesion molecules for inflammatory cells including eosinophils around hair follicles.[5] Other studies have reported that IL-5 level, which induces proliferation and differentiation of eosinophils, is elevated in the blood and skin lesions of patients with EPF, but it can be decreased by treatment with IFN-γ.[6,7] Three members of the eotaxin family—eotaxin-1/CCL11, eotaxin-2/CCL24, and eotaxin-3/CCL26—are known to promote the growth and recruitment of eosinophils and skin inflammation.[8] T_H2 cytokines, such as IL-4, -5, and -13, enhance the production of eotaxins by skin component cells, such as lymphocytes, macrophages, endothelial cells, fibroblasts, and keratinocytes.[9-11] These findings suggest that the pathogenesis of EPF consists of a T_H2-type immune response; intriguingly, however, EPF is usually resistant to topical or systemic corticosteroids that suppress the functions of T cells. Therefore, the pathogenesis of EPF might not be explained solely by T_H2 immunity. Since EPF can be successfully treated with indomethacin, a COX inhibitor,[1,2] we hypothesize that the prostaglandin (PG) family known as the prostanoids, which occur downstream of COX, might be involved in the etiology of EPF.

Prostanoids are released from cells immediately after their formation. Because they are chemically and metabolically unstable, they usually function only locally through membrane receptors on target cells.[12] Recently, individual prostanoid receptor gene–deficient mice have been used as models to dissect the respective roles of each receptor in combination with the use of compounds that selectively bind to prostanoid receptors as agonists or antagonists.[14,15] The prostanoids PGD_2 and PGF_2 are 2 of the major COX metabolites in the skin. PGF_2 has been reported to have an inhibitory effect on eosinophil trafficking and

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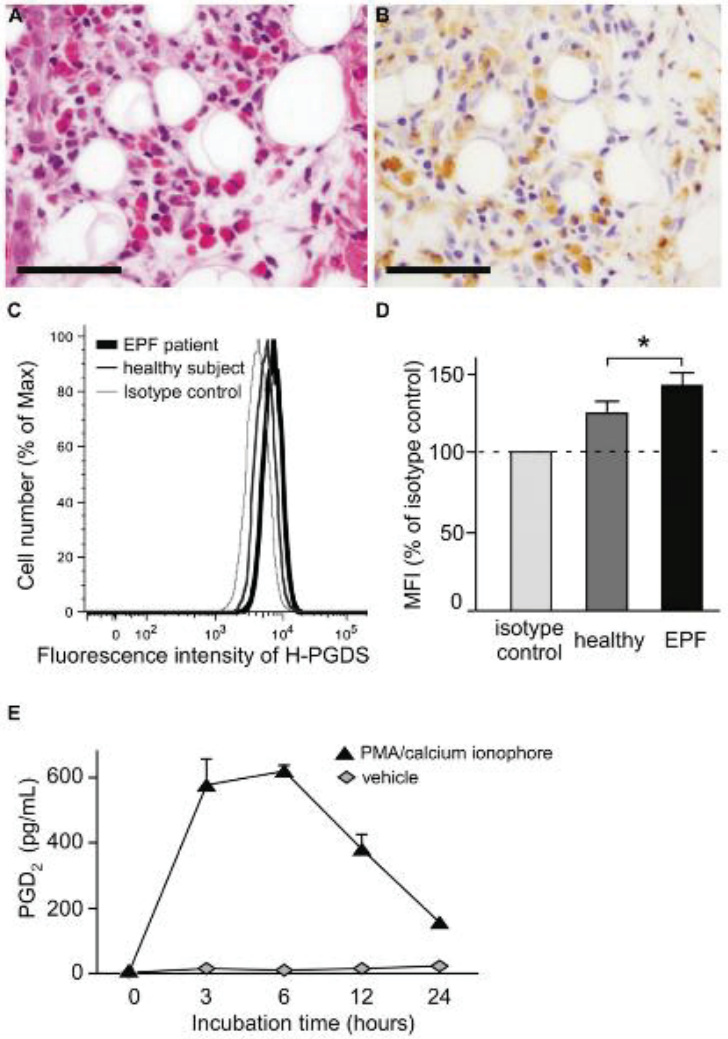
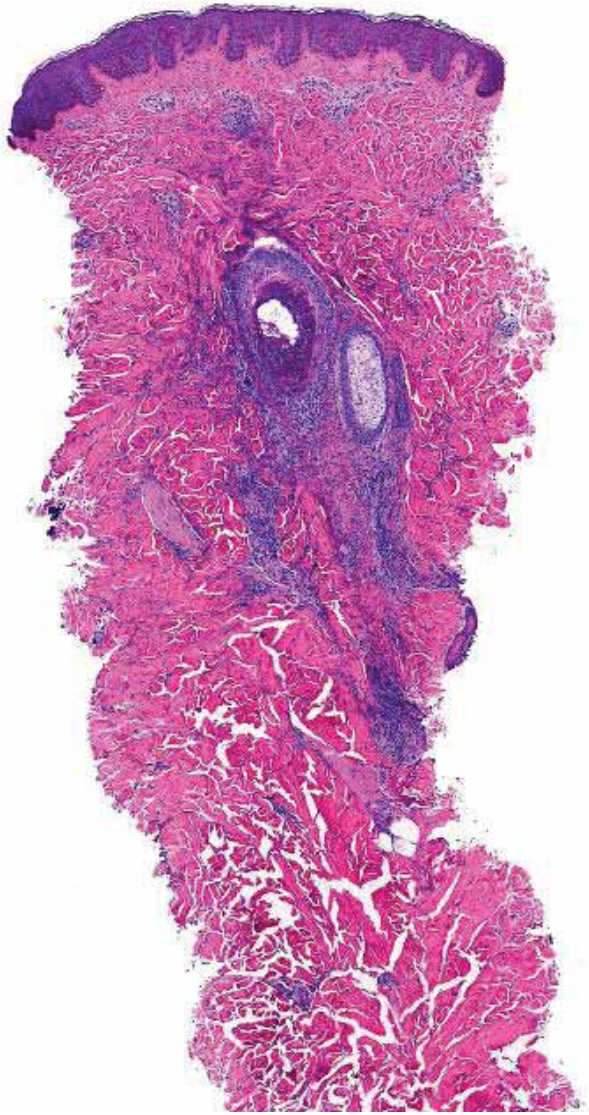
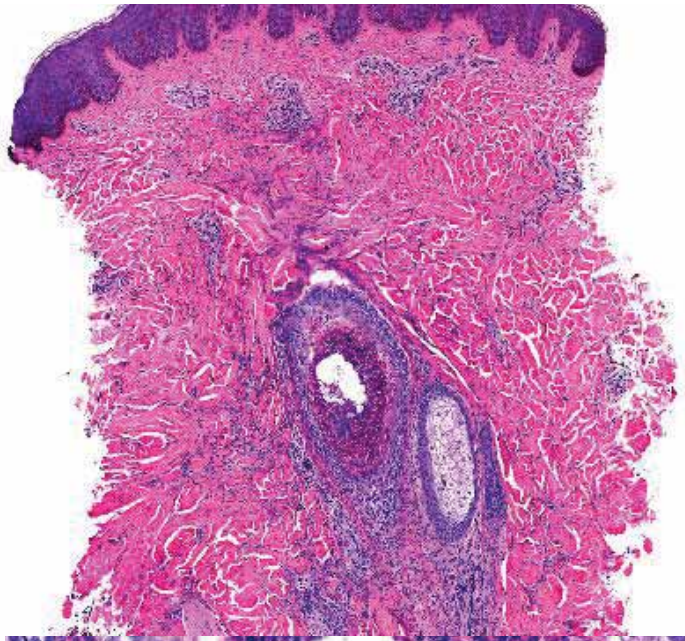
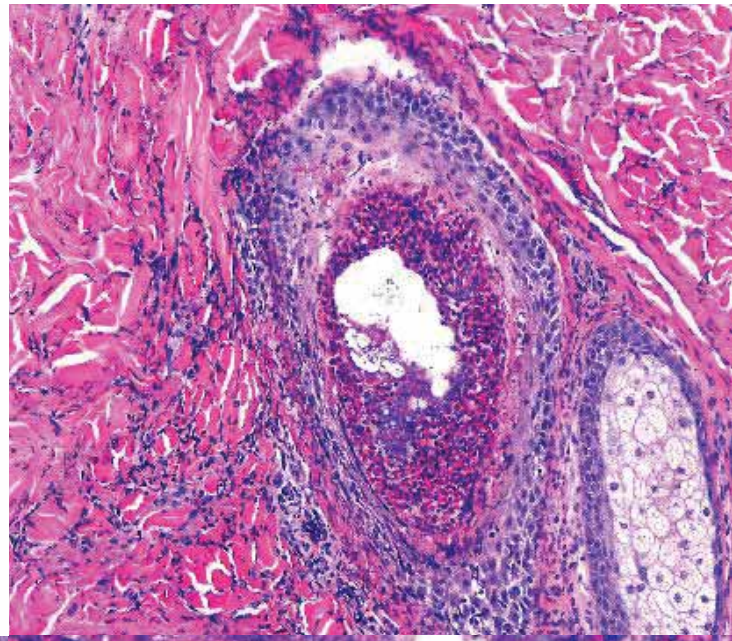
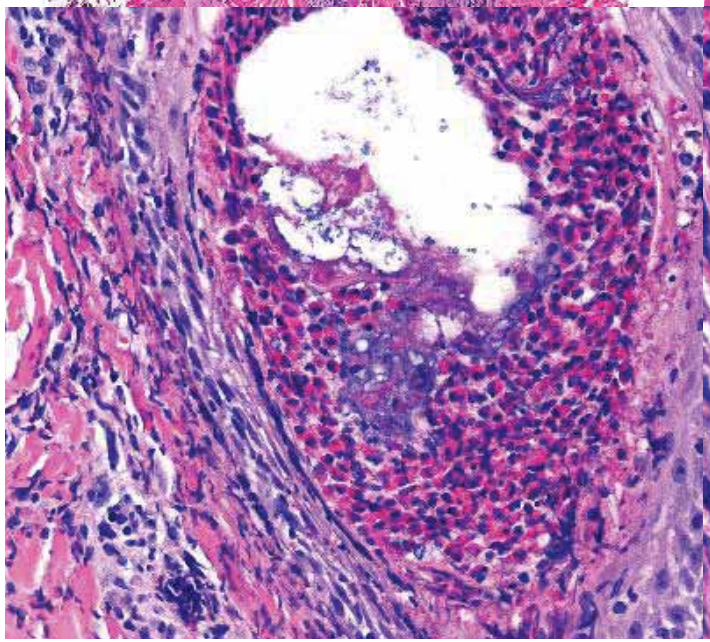
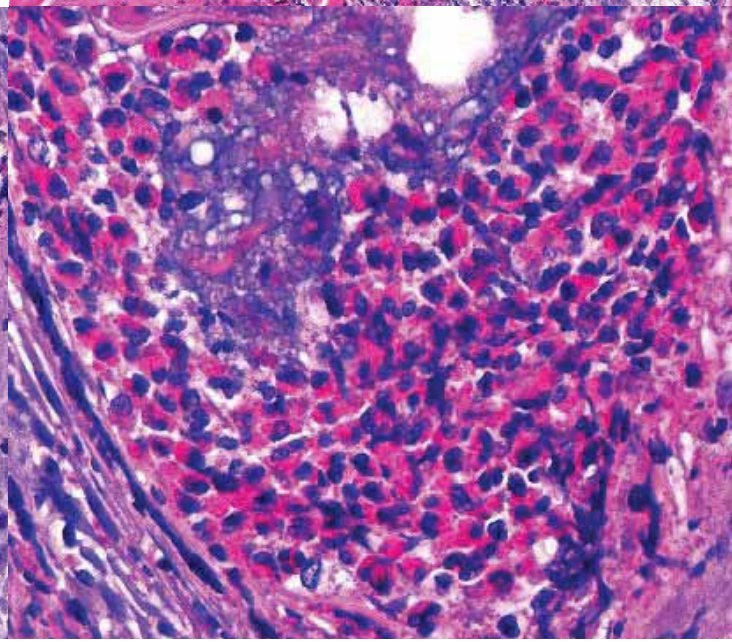
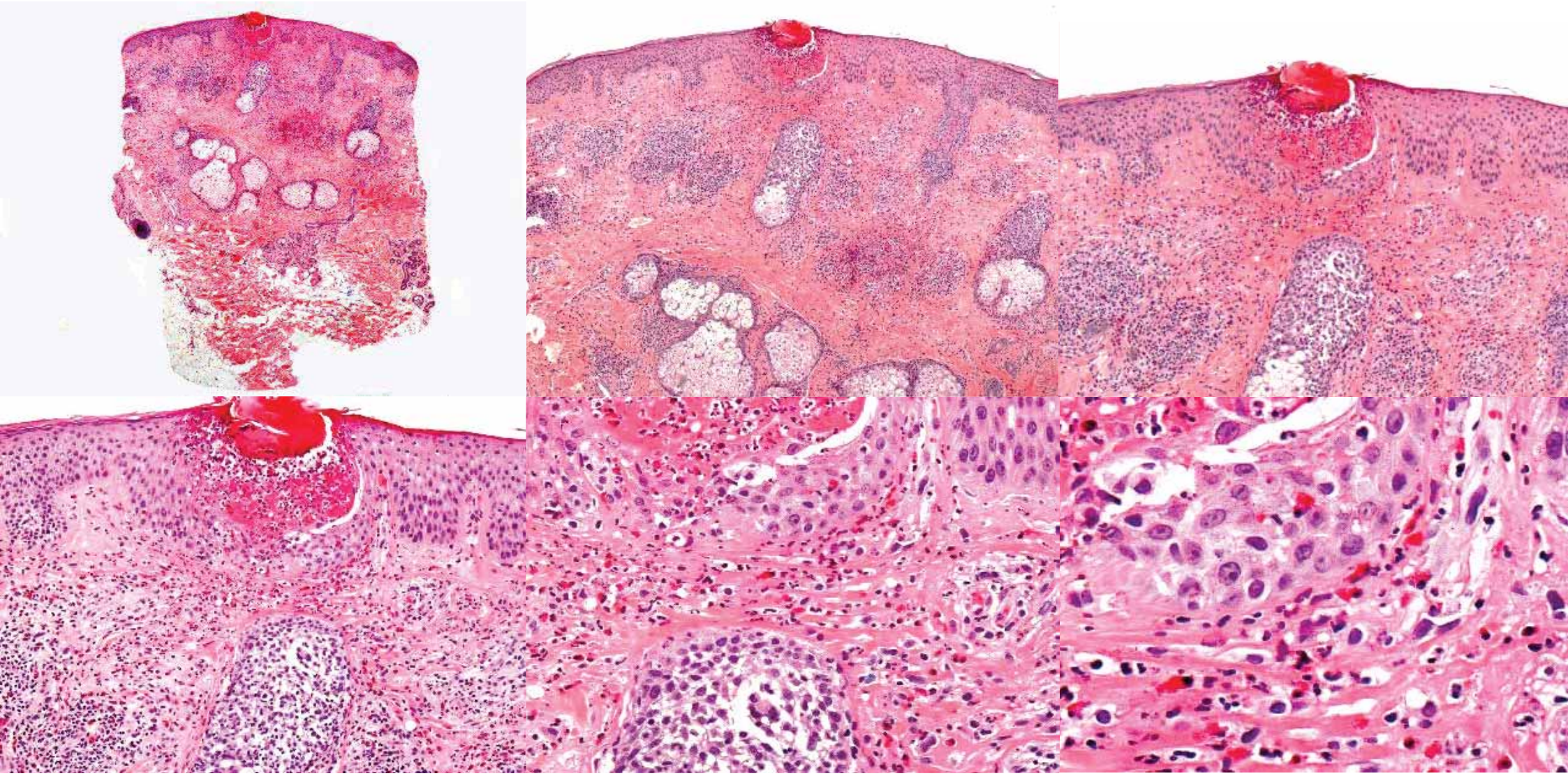


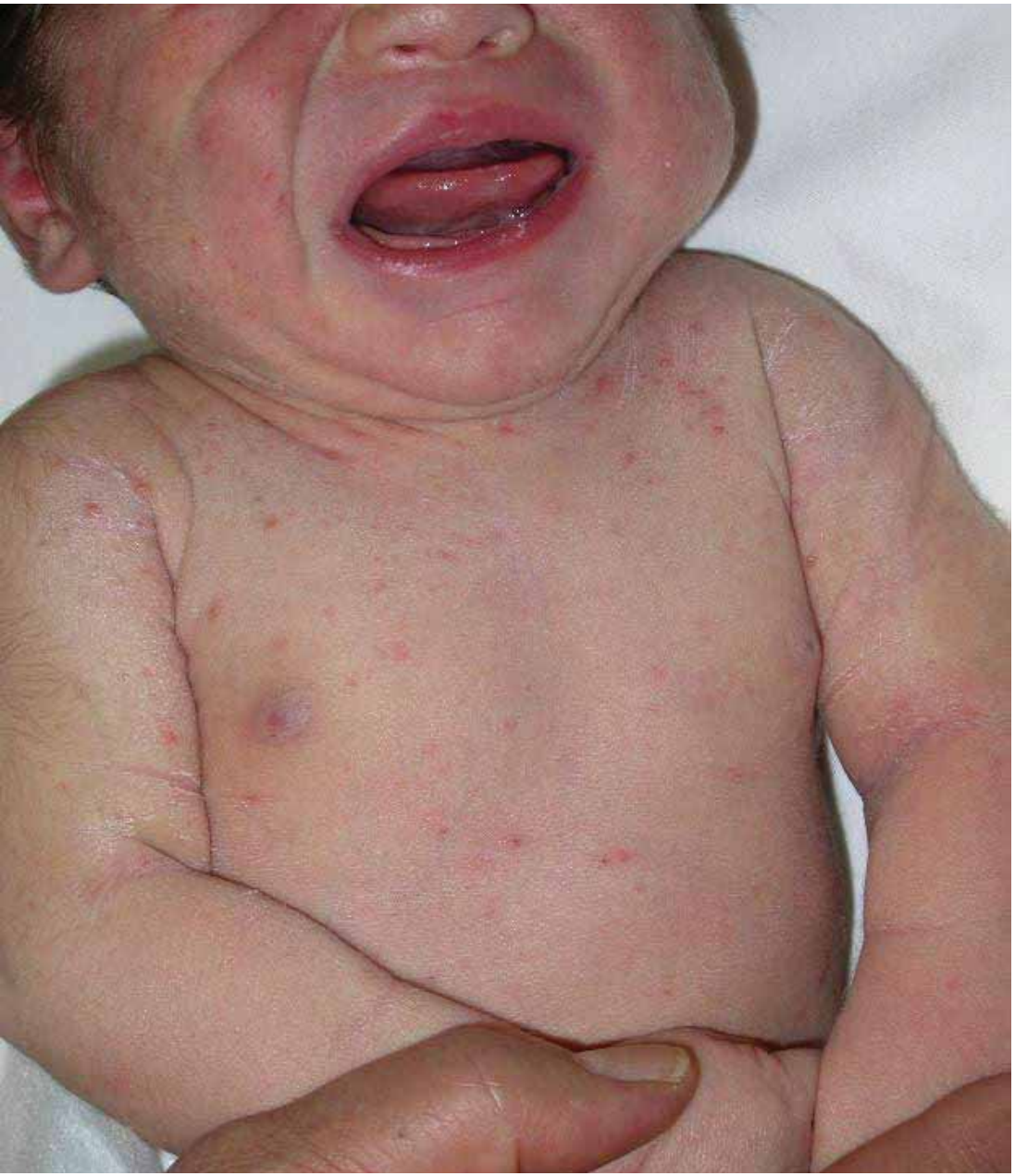
FIG 2. H-PGDS expression and PGD_2 production in eosinophils. Skin specimens of patients with EPF were stained with hematoxylin-eosin **(A)** and anti–H-PGDS antibody **(B)**. Bar = 100 μm. H-PGDS expression in eosinophils was determined by flow cytometry. **C,** Representative flow cytometry results. **D,** The MFI of isotype control was set as 100%, and the MFI of H-PGDS was calculated accordingly (n = 3). *$P < .05$. **E,** PGD_2 levels in eosinophil culture supernatants with or without phorbol 12-myristate 13-acetate and calcium ionophore. *MFI,* Mean fluorescence intensity.



EOSINOPHILIC DERMATOSES

Eosinophil location	Clinical pattern	Disorder
Epidermis	Eczematous	Atopic dermatitis Contact dermatitis Cutaneous T cell lymphoma Hypereosinophilic syndrome with cutaneous manifestations Langerhans cell histiocytosis Scabies and larva migrans
Dermo-epidermal junction	Macular and papular	Drug eruption DRESS
Papillary dermis	Urticarial	Urticaria Eosinophilic cellulitis (Wells syndrome) Episodic angioedema with eosinophilia (Gleich syndrome) Polymorphic eruption of pregnancy
Subepidermal/papillary dermis and hair follicles	Blisters and pustules	Bullous pemphigoid Pemphigus Incontinentia pigmenti Eosinophilic pustular folliculitis Erythema toxicum neonatorum
Papillary and reticular dermis	Papular and nodular	Insect bite Prurigo nodularis Eosinophilic annular erythema Eosinophilic cellulitis (Wells syndrome) Angiolymphoid hyperplasia with eosinophilia and Kimura disease Eosinophilic dermatosis associated with hematologic malignancy Primary cutaneous CD30+ lymphoproliferative disorders
Subcutis	Panniculitic	Erythema nodosum Parasitic panniculitis
Superficial vascular dermal plexus	Vasculitic	Eosinophilic vasculitis Granuloma faciale Eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease)
Fascia	Fibrosis and sclerosis	Localized scleroderma Systemic sclerosis Eosinophilic fasciitis



Histopathology of Erythema Toxicum Neonatorum

ROBERT G. FREEMAN, M.D.; RACHEL SPILLER, M.D., and JOHN M. KNOX, M.D., Houston, Texas

Erythema toxicum neonatorum is a common condition, occurring in approximately one-third of the infants examined by Taylor and Bondurant.[1] These authors gave the first presentation of this disease in the American dermatological literature, emphasized that erythema toxicum neonatorum is a definite disease entity, and gave an excellent description of the clinical picture. The disease appears within the first three to four days of life as erythematous macules, papules, pustules, or combinations of these lesions. The eruption generally disappears by the sixth day of life. Lüders[2] recently reported the first description of the histologic changes that occur with the disease. The present paper presents our histopathologic findings in 10 cases.

Material and Methods

The present study was performed on biopsy tissues obtained from 10 erythema toxicum neonatorum patients showing typical erythematous, papular, or pustular lesions. Cases were selected to show early and late lesions of all forms, including three predominantly erythematous, three predominantly papular, two papulopustular, and two pustular lesions. The biopsies were performed in the routine manner using a 4 mm. biopsy punch. Each specimen of tissue was fixed in 10% formalin, embedded in paraffin, serially sectioned, and stained with hematoxylin and eosin. Every third section was stained with periodic acid-Schiff technique.

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From the Departments of Dermatology and Pathology, Baylor University College of Medicine, Houston.

Results

The histopathologic findings were as follows:

1. *Macules and Erythematous Areas.*—The changes consisted of edema in the upper dermis associated with a mild cellular infiltration that was perivascular and diffuse in distribution. The infiltrating cells were predominantly eosinophilic leukocytes plus a few neutrophilic leukocytes and mononuclear cells (Fig. 1). While hair follicles and sweat glands were seen in involved areas, there was no clear relation of these

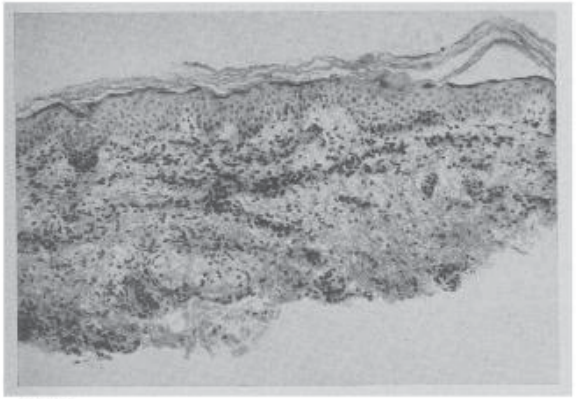

Fig. 1.—Section from a macular lesion. There is edema in the upper dermis and a diffuse and perivascular infiltrate of eosinophils.

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Annual Erythema of Infancy

Alexander G. Peterson, Jr, MD; Michael Jarrett, MD

● The lesions of an unusual annular erythema in an infant evolved from erythematous papules, in rings, to interrupted arcs over 36 to 48 hours, and then resolved without a trace. New lesions appeared and evolved with remarkable uniformity for eight months and then disappeared. This seemingly unique eruption is compared with other annular erythemas described in infants.

(Arch Dermatol 1981;117:163-165)

The annular erythemas described in infants and children include erythema annulare centrifugum, familial annular erythema,[1] erythema gyratum atrophicans transiens neonatale,[2] and erythema chronicum migrans with Lyme arthritis.[3] To our knowledge, erythema gyratum repens has not yet been described in the pediatric age group.

The lesions of erythema annulare centrifugum begin as erythematous, urticarial papules on the trunk that enlarge centrifugally to form rings and arcs 10 cm or more in diameter. The advancing urticarial margin may be topped by microvesicles or followed by a fine collarette of scale. While individual lesions usually resolve in days to weeks, the disease may last two years or longer. Darier[4] coined the term "erythema annulare centrifugum" in 1916, but similar lesions were previously described under a variety of names by several authors. Wende[5] noted no specific age or sex predisposition, but reported that cases rarely began at birth. Fried et al[6] described an infant in 1957 who had what they called "erythema annulare centrifugum." Erythema annulare centrifugum may occur with an underlying malignant neoplasm or with a variety of infections, including *Candida* infection, meningitis, tuberculosis, streptococcal disease, dental infection,[7] Epstein-Barr virus infection,[8] and with diarrhea, eosinophilia, and fibrosing alveolitis.[9] Cases have been reported secondary to trichophytin skin testing,[4] maternal autoimmune disease,[5] and ingestion of salicylates,[10] blue cheese *Penicillium*,[11] tomatoes,[4] and hydroxychloroquine sulfate and chlorquine sulfate.[12]

Familial annular erythema was originally described as erythema gyratum perstans by Calcott Fox[13] in 1891. The eruption usually begins shortly after birth as erythematous, urticaria, papules that enlarge centrifugally to form rings with vesiculated borders or an inner collarette of scale. Beare et al[14] reported familial annular erythema in an infant and two members of the same family. The disorder lasted many years and was characterized by lesions that disappeared after four or five days, leaving a transient, brownish pigmentation. The eruption appeared in one patient at a few days of age and showed no desquamation or vesiculation. The older relative outgrew his disease. The syndrome included decreased α_1- and α_2-globulins and an increased serum IgA level.[15] Geographic tongue may also be present in this disorder.[16]

Erythema gyratum atrophicans transiens neonatale is a disease of newborns. It begins as a generalized, patchy, erythematous eruption that resolves into atrophic and hypopigmented lesions. Histologically, epidermal atrophy, dermal edema, and a mononuclear cell infiltrate are present. Immunofluorescence microscopy reveals granular deposits of IgG, C3, and C4 at the dermoepidermal junction and around the superficial capillaries.[2]

Erythema chronicum migrans, first described by Afzelius[17] and Lipschütz,[18] begins around the site of an arthropod bite. The lesion slowly enlarges centrifugally as a blue-red urticarial ring that is free of scale. The lesion may attain a diameter of up to 20 or 30 cm. A central punctum, the site of the inciting tick or mosquito bite, may be present. Without treatment, the lesion may persist for months to years.[3,19] Only a single lesion is observed in most cases. Scrag[20] notes that, in his series of 45 cases, there were two or more rings in only four patients. The eruption may be accompanied by pruritus, hypoesthesia, myalgia, malaise, fever, lymphadenopathy, and meningoencephalomyelitis.[21] Histologically, a mononuclear perivascular and perivascular dermal infiltrate is present.[22] Ticks of the genus *Ixodes*, as well as mosquitoes, transmit the disease. There is often a dramatic response to antibiotics. Erythema chronicum migrans occurs chiefly in Europe and Scandinavia, although cases have been reported in the United States as well.[3,19]

Since 1965, more than 400 cases of erythema chronicum migrans have been reported in the United States in association with Lyme arthritis.[3,19] Lyme arthritis, first described in 1976 in Lyme, Conn, is characterized by recurrent, brief episodes of asymmetric, oligoarticular pain and swelling in the large joints. Twenty-five percent of the patients report a preceding episode of erythema chronicum migrans. The skin lesions last three days to eight weeks, with a median of three weeks. Malaise, fever, chills,

Accepted for publication June 20, 1980.

From the Department of Dermatology, Baylor College of Medicine, Houston.

Reprints not available.

Annular Erythema of Infancy

Alexander O. Peterson, Jr, MD, Michael Jarratt, MD

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(Arch Dermatol 1981;117:145-148)

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Familial annular erythema was originally described as erythema gyratum perstans by Colcott Fox[14] in 1891. The eruption usually begins shortly after birth as erythematous, urticarial papules that enlarge centrifugally to form rings with vesiculated borders or an inner collarette of scale. Beare et al[15] reported familial annular erythema in an infant and two members of the same family. The disorder lasted many years and was characterized by lesions that disappeared after four or five days, leaving a transient, brownish pigmentation. The eruption appeared in one patient at a few days of age and showed no desquamation or vesiculation. The older relative outgrew his disease. The syndrome included decreased α_1- and α_2-globulins and an increased serum IgA level.[15] Geographic tongue may also be present in this disorder.[15,16]

Erythema gyratum atrophicans transiens neonatale is a disease of newborns. It begins as a generalized, patchy, erythematous eruption that resolves into atrophic and hypopigmented lesions. Histologically, epidermal atrophy, dermal edema, and a mononuclear cell infiltrate are present. Immunofluorescence microscopy reveals granular deposits of IgG, C3, and C4 at the dermoepidermal junction and around the superficial capillaries.[2]

Erythema chronicum migrans, first described by Afzelius[17] and Lipschutz,[18] begins around the site of an arthropod bite. The lesion slowly enlarges centrifugally as a blue-red urticarial ring that is free of scale. The lesion may attain a diameter of up to 20 or 50 cm. A central punctum, the site of the inciting tick or mosquito bite, may be present. Without treatment, the lesion may persist for months to years.[3,19] Only a single lesion is observed in most cases. Screk[19] notes that, in his series of 45 cases, there were two or more rings in only four patients. The eruption may be accompanied by pruritus, hyperesthesia, myalgia, malaise, fever, lymphadenopathy, and meningopolyneuritis.[20] Histologically, a mononuclear perisappendageal and perivascular dermal infiltrate is present.[21] Ticks of the genus *Ixodes*, as well as mosquitoes, transmit the disease. There is often a dramatic response to antibiotics. Erythema chronicum migrans occurs chiefly in Europe and Scandinavia, although cases have been reported in the United States as well.[22,23]

Since 1965, more than 400 cases of erythema chronicum migrans have been reported in the United States in association with Lyme arthritis.[3,24] Lyme arthritis, first described in 1976 in Lyme, Conn, is characterized by recurrent, brief episodes of asymmetric, oligoarticular pain and swelling in the large joints. Twenty-five percent of the patients report a preceding episode of erythema chronicum migrans. The skin lesions last three days to eight weeks, with a median of three weeks. Malaise, fever, chills,

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Treatment of Eosinophilic Annular Erythema with Chloroquine

Sir,

Figurate or gyrate erythemas include a variety of dermatoses characterized clinically by annular and polycyclic erythemas or plaques with a tendency to centrifugal extension and central healing. In most cases the aetiology remains unknown and elimination of the cause is then not possible. In some cases spontaneous remission of the different types of gyrate erythemas has been observed (1).

Several drugs have been used previously for the treatment of gyrate erythemas, in particular systemic steroids (2). In most cases, there is a poor response or lesions recur after discontinuation of treatment. Recently, chloroquine has been used as an alternative drug in the treatment of figurate erythemas. Franz et al. (3) observed a patient with erythema annulare centrifugum who showed a good response to chloroquine and hydroxychloroquine with disappearance of skin lesions and no recurrence.

Figurate erythemas with conspicuous tissue eosinophilia have only been reported in children (1, 4). We observed a patient with recurrent annular erythemas, histologically presenting as eosinophilic dermatosis of 9 years' duration; an entity that has to our knowledge not yet been reported in adults. This dermatosis responded only temporarily to corticosteroids, but resolved promptly after treatment with chloroquine.

CASE REPORT

A 56-year-old woman had suffered from recurrent, itchy urticarial papules and annular erythemas up to 10 cm in diameter on the trunk and extremities for 9 years starting in 1989 (Fig. 1). At first presentation, the annular erythemas were slightly scaling. There was a history of thyroiditis and thyrostatic treatment 10 years previously. She had not been taking any drugs during that time. Several laboratory and clinical work-ups were done in that period and revealed normal laboratory data and blood chemistry including eosinophil count, except for an elevated white blood cell count of $11500/mm^3$. Antinuclear antibodies and subsets, electrophoresis and immunoelectrophoresis were normal. At the latest examination in 1997 IgG antibodies against *Borrelia burgdorferi* were (1:1...) positive as well as anti-thyroglobulin antibodies with euthyreotic function. Chest X-ray, gynaecological, urological, throat, nose and ear examination, as well as an abdominal ultrasound investigation, were normal. A gastroscopy showed erosions in the antrum (*Helicobacter pylori* negative); furthermore, chronic tonsillitis was diagnosed. Six biopsies, taken at regular intervals during the 9 years, showed a dense superficial and deep perivascular lymphohistiocytic infiltrate in the dermis with abundant eosinophils throughout the dermis, and a normal epidermis and adnexa (Fig. 2). Direct immunofluorescence from one of the biopsies was negative. A T- and B-cell rearrangement to rule out malignant lymphoma performed on the latest skin biopsy in December 1997 showed a polyclonal proliferation.

The patient was treated repeatedly with local and systemic corticosteroids with only moderate success or short symptom-free periods.

Due to high IgG antibodies against *Borrelia burgdorferi* in 1997, a skin biopsy was cultured for *B. burgdorferi* but was negative. Nevertheless, the patient was treated with ceftriaxone 2 g/day intravenously for 3 weeks and topical steroids in January 1998. The eruptions improved slightly, but there was a complete recurrence 3 weeks later. A therapeutic trial with dapsone initiated 4 weeks after treatment with ceftriaxone had to be discontinued after 6 weeks due to vertigo and lack of response. In May 1998, the patient was put on chloroquine 250 mg/day. After 2 weeks there was complete resolution of skin lesions and chloroquine was discontinued after 1 month. Nine months later, the patient was still free of symptoms.

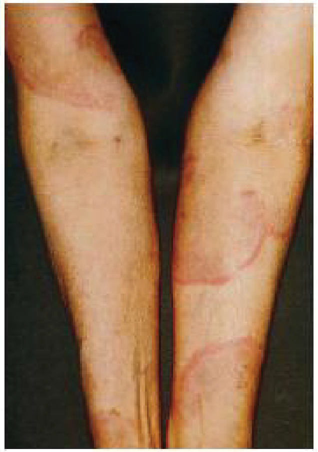

Fig. 1. Several annular plaques on the forearms with central clearing.

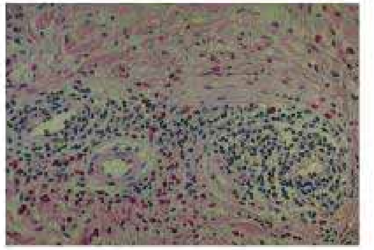

Fig. 2. Dense perivascular mononuclear infiltrate with abundant eosinophils. HE ×25.

DISCUSSION

Although histological investigations of the patient's biopsies were consistent with annular erythemas, the eosinophilic infiltration as well as the clinical picture prompted us to suspect Well's syndrome as a differential diagnosis. Since typical "flame figures" in the biopsy and blood eosinophilia were missing and clinical manifestation and course (absence of prodromal burning, painful oedema, peripheral induration, and subsiding by producing morphea-like lesions) differed from the description in the literature (5), this differential diagnosis was ruled out.

Reviewing the literature, we found that annular erythema of infancy has clinical and histological features similar to those in our patient. In annular erythema of infancy, first described by Peterson & Jarratt in 1981 (4), lesions usually develop from erythematous papules evolving into a palpable erythematous arc or ring, but scaling or vesicles are missing in most cases. Eruption of the lesions is cyclic with persistence of some days up to weeks or months. Histopathological findings show a perivascular infiltrate of lymphocytes and eosinophils. Usually neither underlying disease nor provocative factors were reported and the disease was generally self-limiting (4). In a recent report by Kunz et al. in 1998, annular lesions lasted for 5 years with remissions of several months. Treatment with systemic steroids led to short remissions only and treatment with dapsone was not successful, but there was spontaneous resolution within some weeks after the patient had been seen again at the age of 9 years (1).

Our patient was repeatedly treated with corticosteroids with only temporary success. Since a response to sulfones was reported in patients with eosinophilic dermatoses (6), we also tried this drug; however, it had to be discontinued due to side-effects. In analogy with successful treatment of annular erythema of Sjögren syndrome with anti-malaria drugs (3), we started treatment with chloroquine, although the patient was negative for specific autoantibodies. With a dose of 250 mg chloroquine/day the annular erythemas showed a complete remission after 2 weeks of treatment and did not recur during the observation period of 9 months.

The course of disease in our patient was not unusual. Gyrate erythemas may recur for months and years, especially when the aetiology is unknown. The prompt response to treatment with chloroquine was impressive. As chloroquine is known to inhibit eosinophilotaxis (7), this might have been a possible therapeutic mechanism in our patient. Furthermore, it is known that chloroquine has a dose-dependent inhibitory effect on the release of pro-inflammatory cytokines (8).

There has never yet been described a case report of gyrate erythemas in which eosinophilic granulocytes dominated in the dermal infiltrate. For that reason we assume that our case might be a hitherto unreported entity among the large group of gyrate erythemas.

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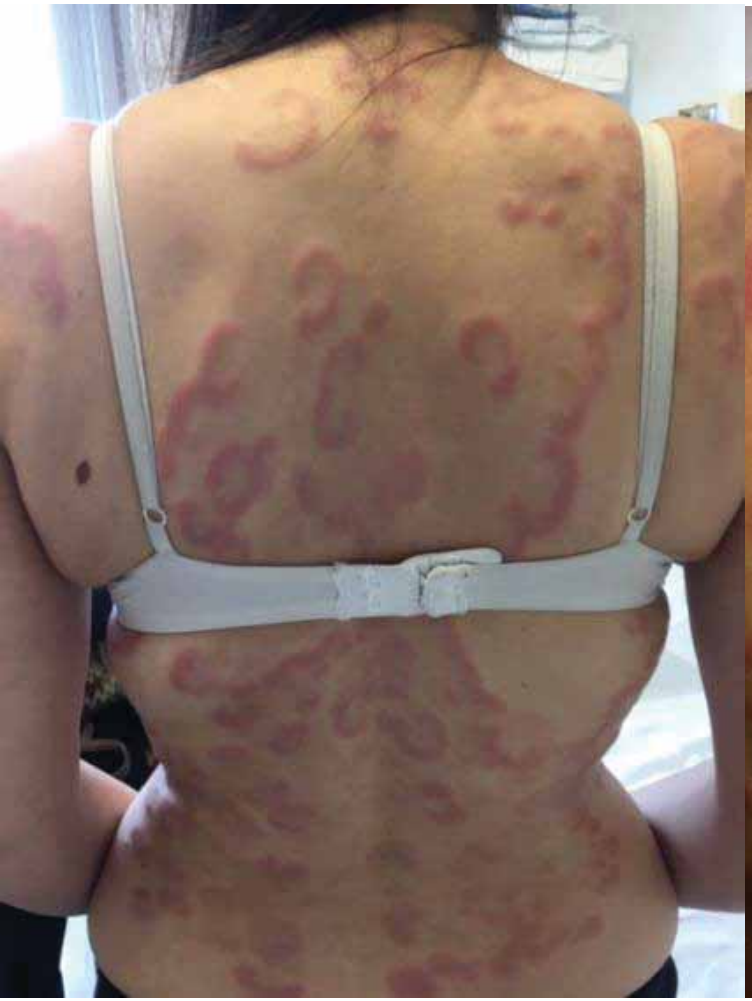
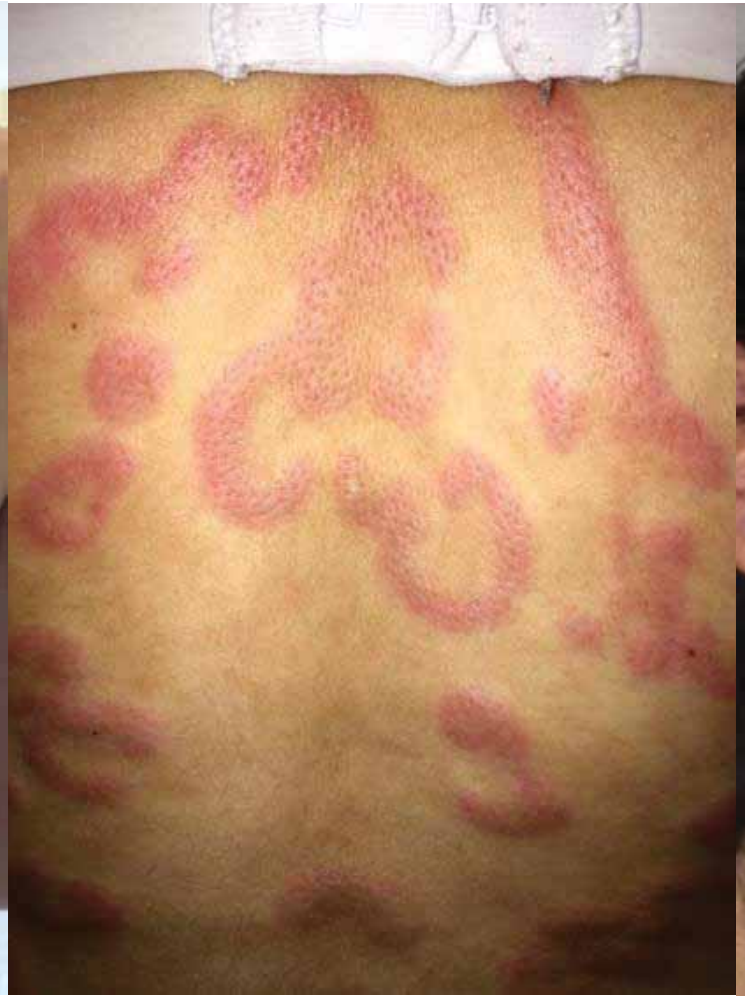


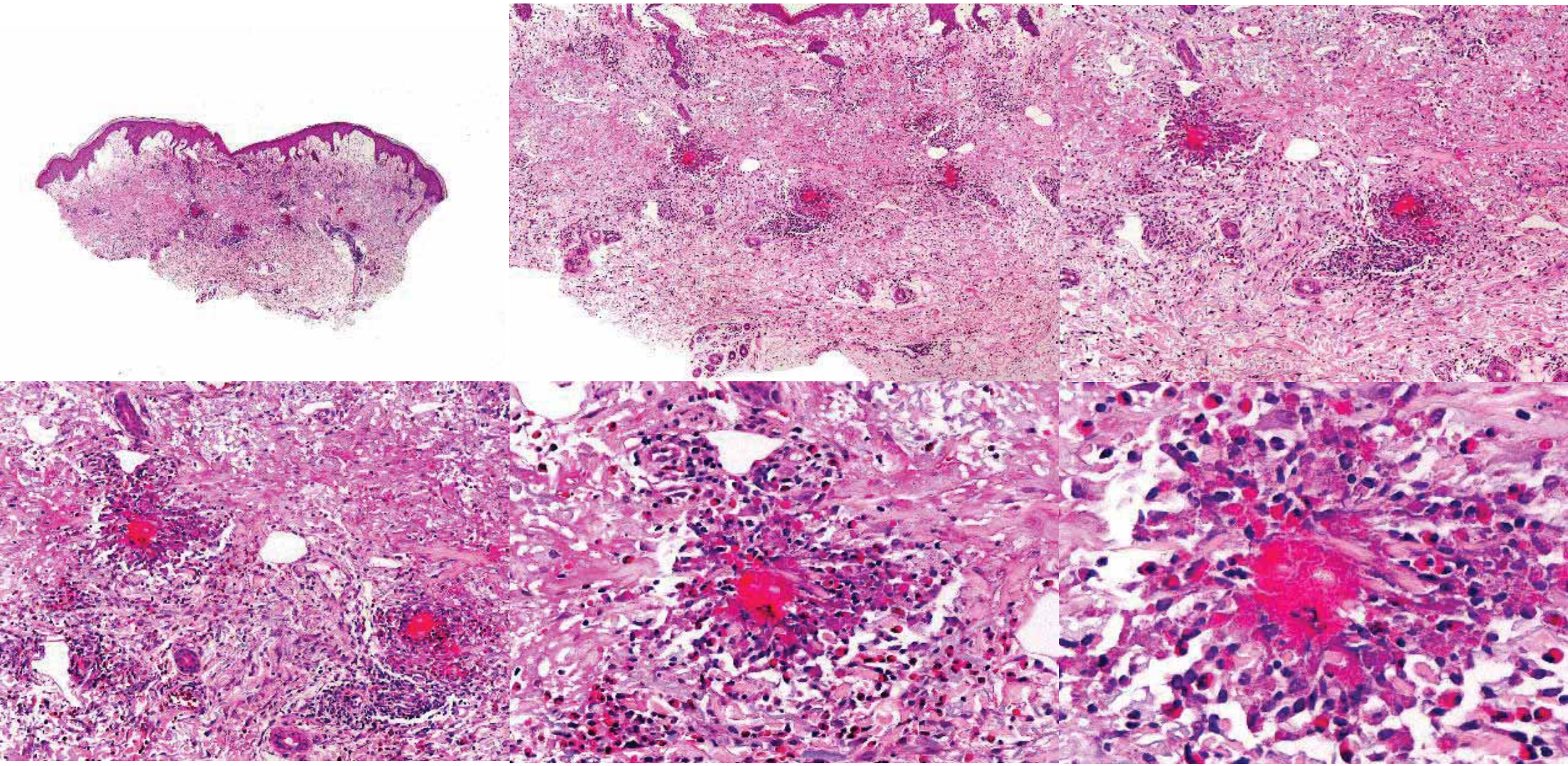

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CASE REPORT

Eosinophilic annular erythema: A subset of Wells' syndrome or a distinct entity?

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SUMMARY

CASE REPORT

INTRODUCTION

letters e155

Eosinophilic annular erythema: An expression of the clinical and pathological polymorphism of Wells syndrome

REFERENCES

JEADV

ORIGINAL ARTICLE

Eosinophilic annular erythema is a peculiar subtype in the spectrum of Wells syndrome: a multicentre long-term follow-up study

M. El Khalawany, N. A. Mutairi, M. Sultan, D. Shaaban

Abstract

Background/Objective Eosinophilic annular erythema (EAE) was proposed to describe annular skin lesions associated with tissue eosinophilia. However, its relation to Well's syndrome (WS) remains a source of controversy. We studied a series of patients to increase awareness of this entity and to clarify its relation to WS.

Conflicts of interest

Introduction

EOSINOPHILIC DERMATOSES

Eosinophil location	Clinical pattern	Disorder
Epidermis	Eczematous	Atopic dermatitis Contact dermatitis Cutaneous T cell lymphoma Hypereosinophilic syndrome with cutaneous manifestations Langerhans cell histiocytosis Scabies and larva migrans
Dermo-epidermal junction	Macular and papular	Drug eruption DRESS
Papillary dermis	Urticarial	Urticaria Eosinophilic cellulitis (Wells syndrome) Episodic angioedema with eosinophilia (Gleich syndrome) Polymorphic eruption of pregnancy
Subepidermal/papillary dermis and hair follicles	Blisters and pustules	Bullous pemphigoid Pemphigus Incontinentia pigmenti Eosinophilic pustular folliculitis Erythema toxicum neonatorum
Papillary and reticular dermis	Papular and nodular	Insect bite Prurigo nodularis Eosinophilic annular erythema Eosinophilic cellulitis (Wells syndrome) Angiolymphoid hyperplasia with eosinophilia and Kimura disease Eosinophilic dermatosis associated with hematologic malignancy Primary cutaneous CD30+ lymphoproliferative disorders
Subcutis	Panniculitic	Erythema nodosum Parasitic panniculitis
Superficial vascular dermal plexus	Vasculitic	Eosinophilic vasculitis Granuloma faciale Eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease)
Fascia	Fibrosis and sclerosis	Localized scleroderma Systemic sclerosis Eosinophilic fasciitis

Br. J. Derm. (1969) **81**, 1.

St. Thomas's Hospital and St. John's Hospital for Diseases of the Skin, London

SUBCUTANEOUS ANGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA

G. C. WELLS AND I. W. WHIMSTER

SUMMARY.—Persistent subcutaneous nodules on the head and neck with distinctive histological features of angiolymphoid hyperplasia with eosinophilia are reported in nine patients. They were all young adults and had one or more lesions ranging from 1 to 10 cm. in diameter. Apart from blood eosinophilia, there were no systemic manifestations. While some lesions persisted for several years, the condition appears to be benign. The nodules lie mainly in the subcutis but sometimes extend into the overlying dermis and deeply into muscle or fascia. They are composed of unencapsulated masses of angiolymphoid hyperplasia with the following components:

1. **Exuberant proliferation of capillary vessels, often with imperfectly canalized masses of endothelium.**
2. **Massive infiltration with eosinophils and an excess of mast cells.**
3. **Reticulin formation but little collagenous fibrosis.**
4. **Lymphoreticular hyperplasia, increasing with the duration of the lesion and leading to lymphoid follicle formation in lesions of one year or more duration.**

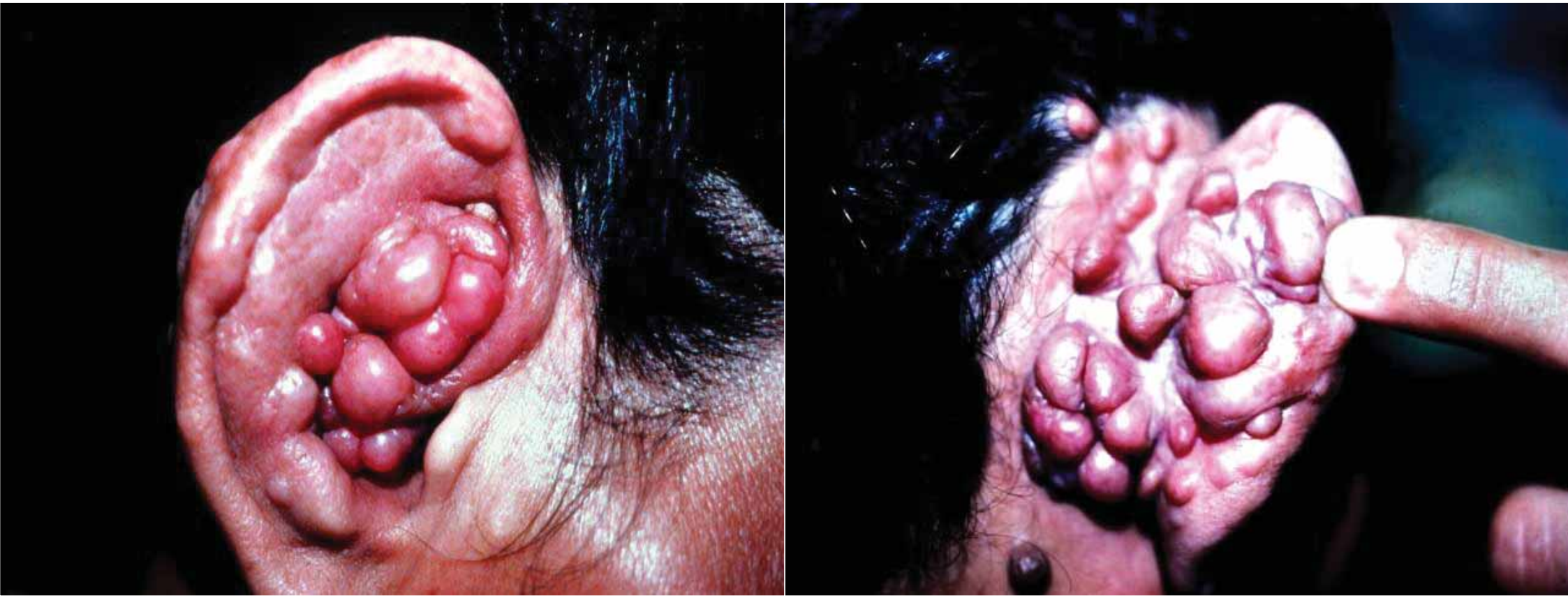
The clinical and histological features suggest enough common ground for regarding subcutaneous angiolymphoid hyperplasia with eosinophilia as a distinct pathological entity. Its relation to Kimura's disease as described in Japan is discussed.

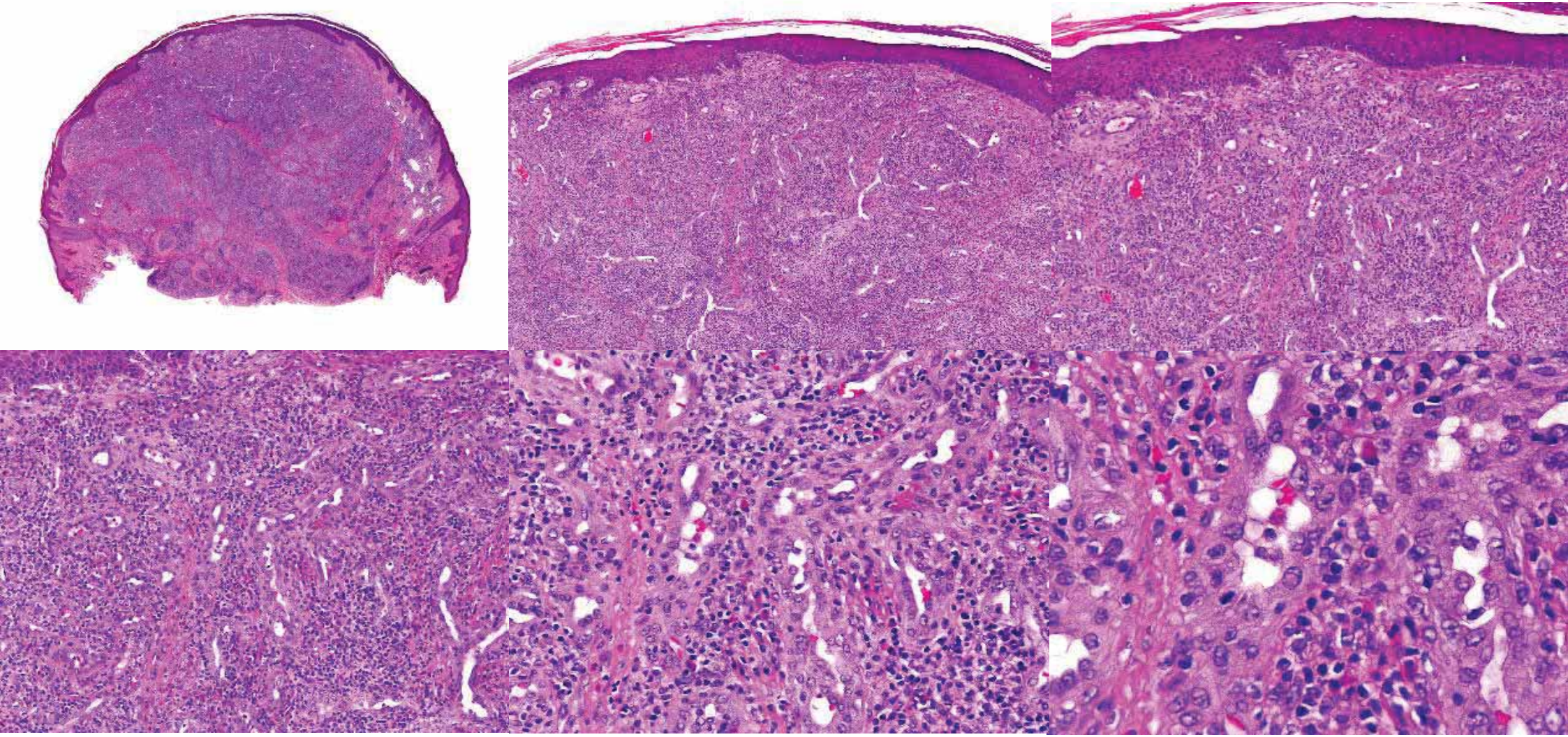
THE following account of the clinical and histological findings of subcutaneous angiolymphoid hyperplasia in 9 patients is presented in the hope that other cases will be recognized and some understanding of the pathogenesis may accrue. We are conscious of our debt to many colleagues who referred histological material and provided clinical information, as indicated at the end of this paper.

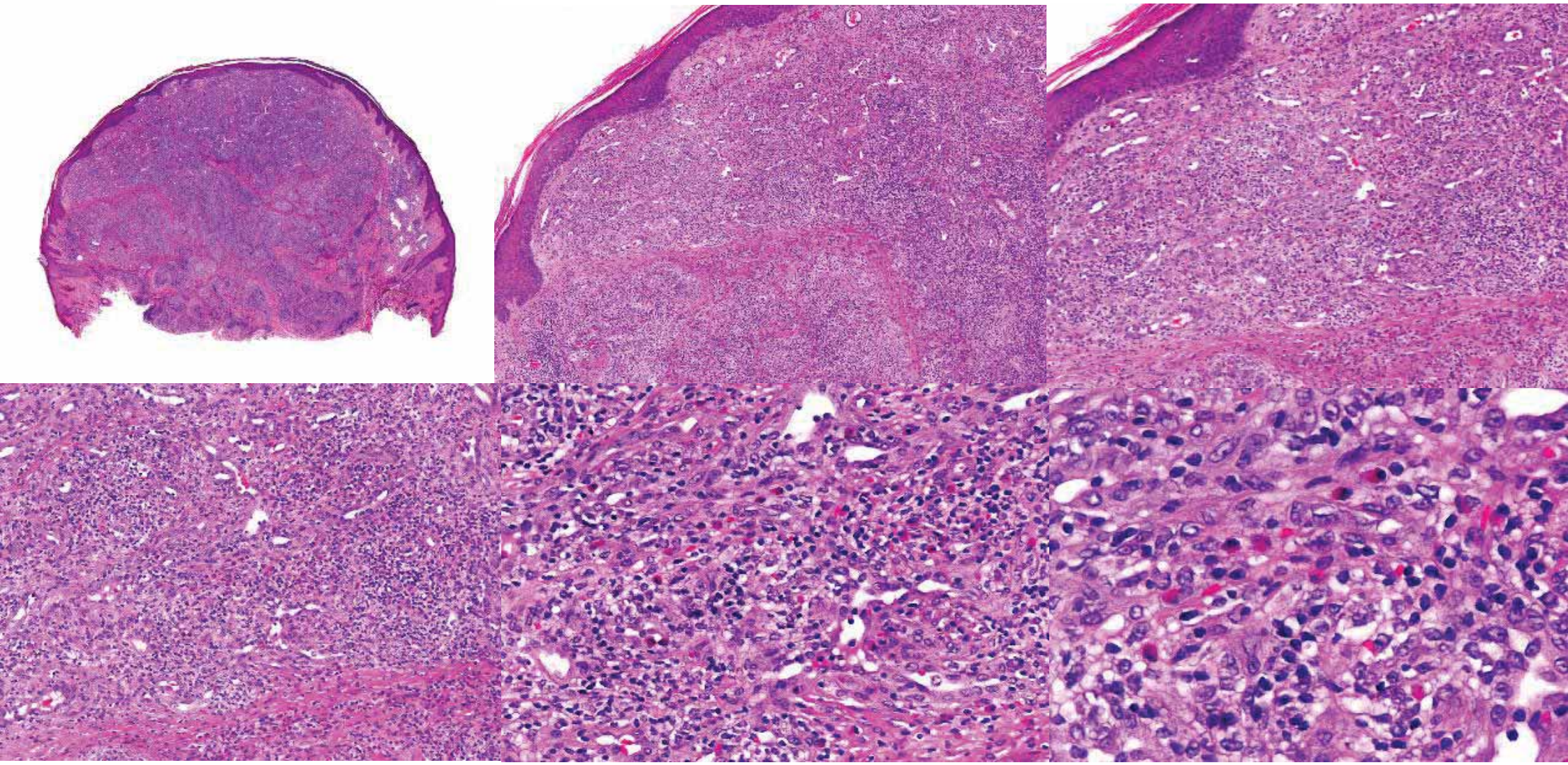
Case No. 1

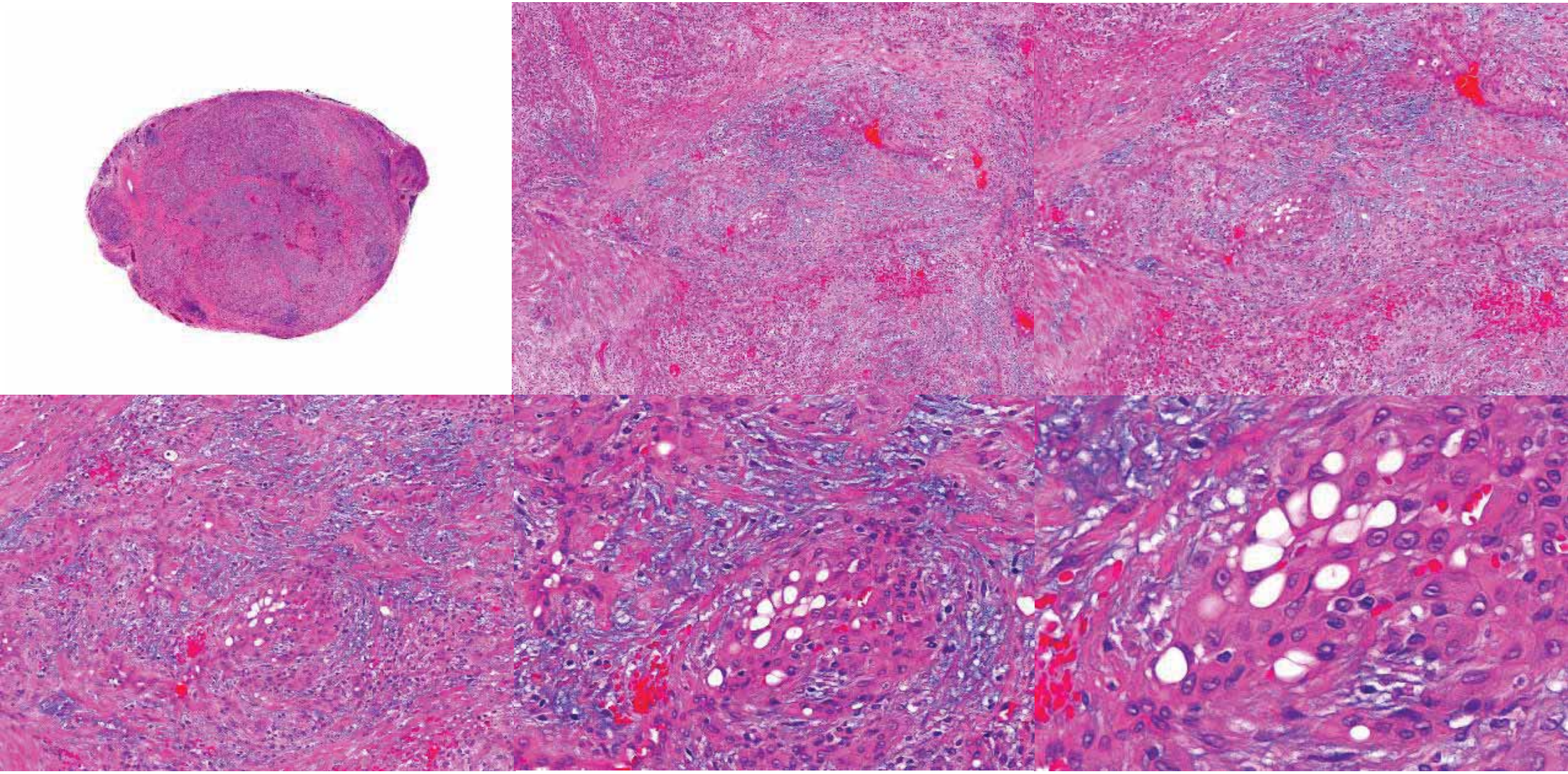
A 43 year old housewife attended St. Thomas's Hospital in 1952 with a lump behind the left ear. This had first been noticed a year before and had gradually enlarged to 2·5 cm. in diameter. Her general health had been good, apart from an abscess of the right side of the neck drained at the age of 3. She had not lived outside England and there was no history of trauma or insect bites on the area affected.

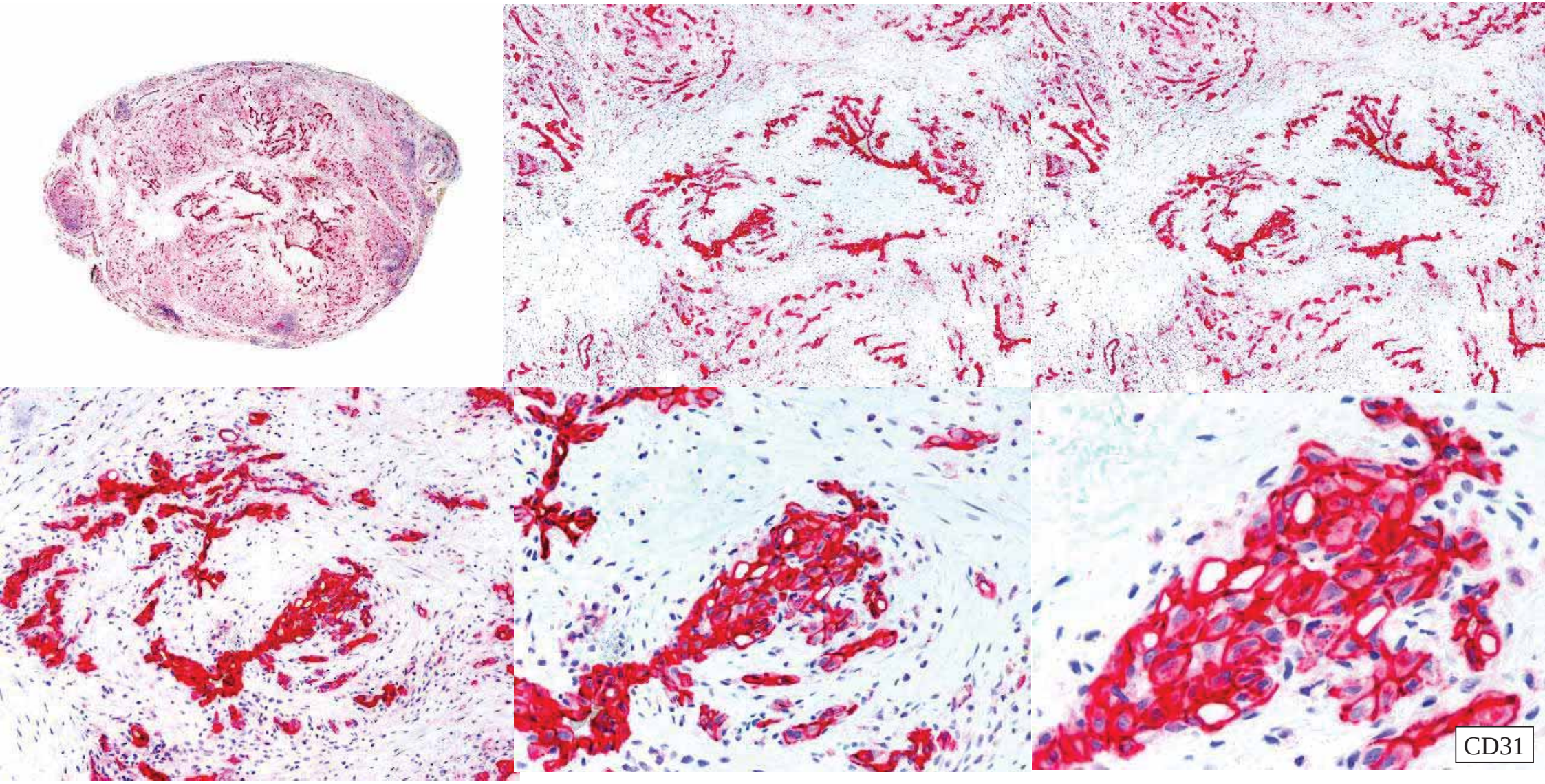
She was noted to have 3 subcutaneous nodules on the left side of the face, one retro-auricular, one sub-auricular and one at the angle of the jaw. She noticed some itching from time to time in association with these lesions. There were no enlarged lymph nodes in other parts of the body and the spleen was not palpable. Chest x-ray normal. Blood WR negative. The nodule from the left retro-auricular region was excised in 1952.







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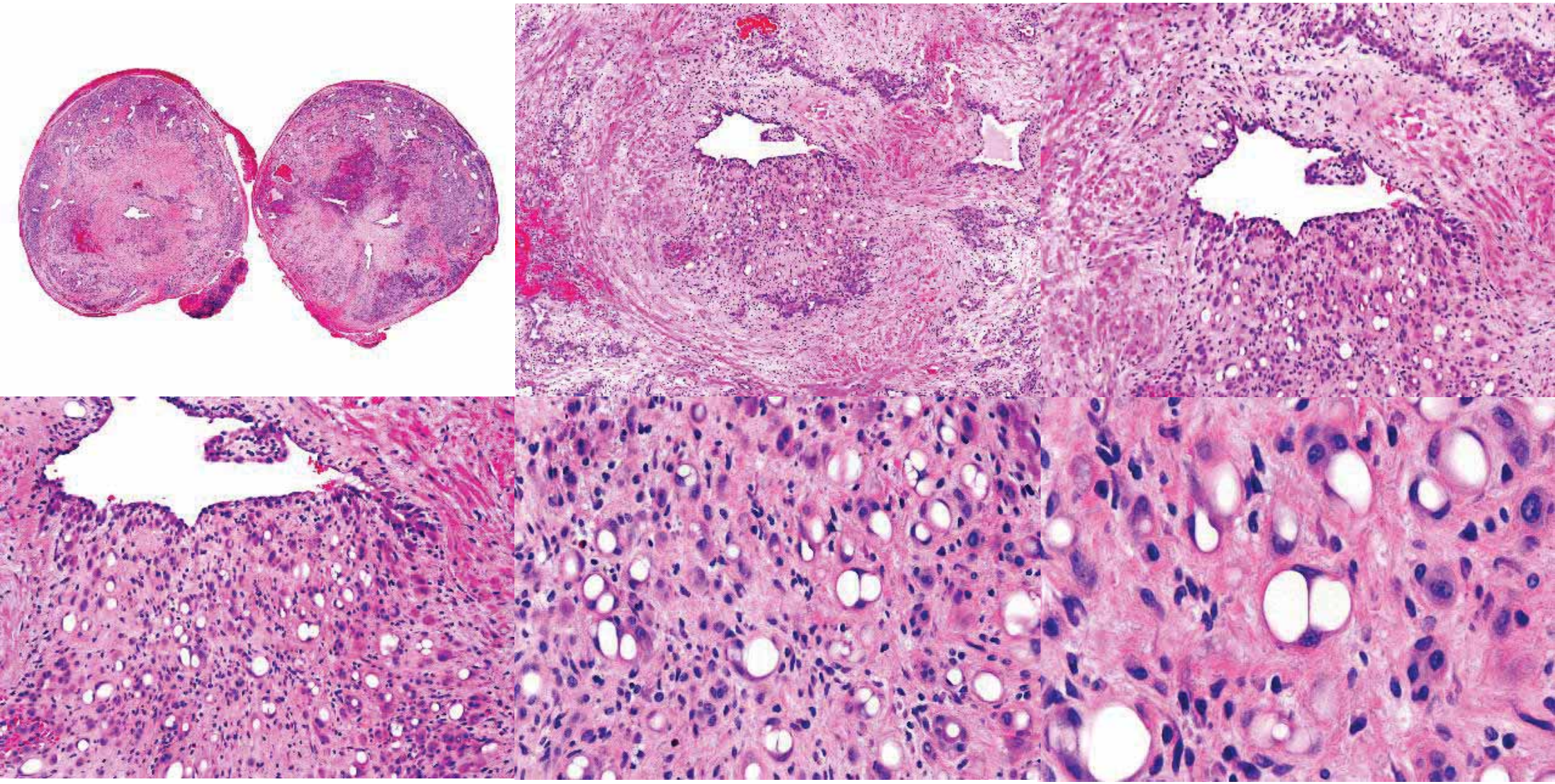

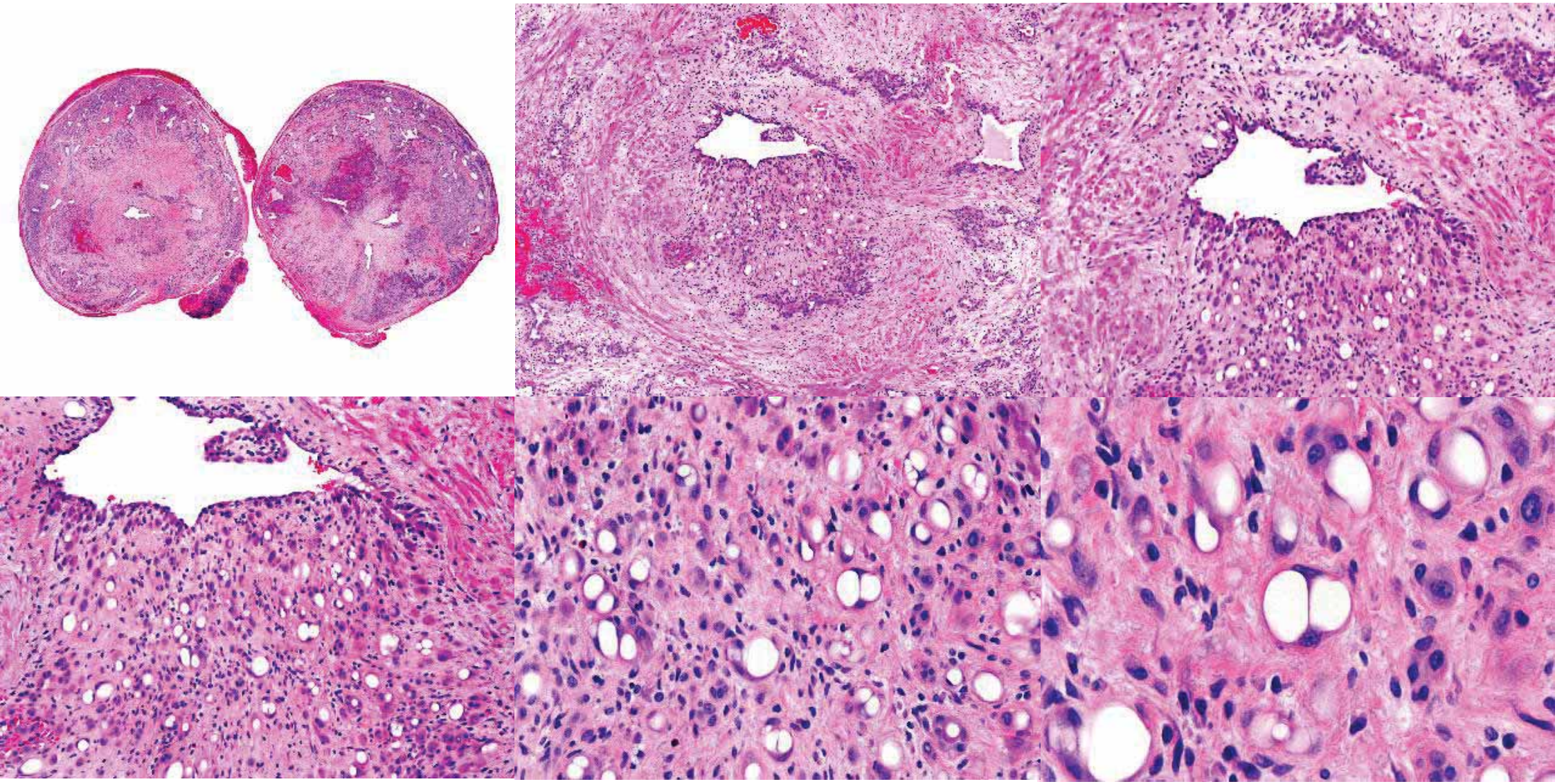

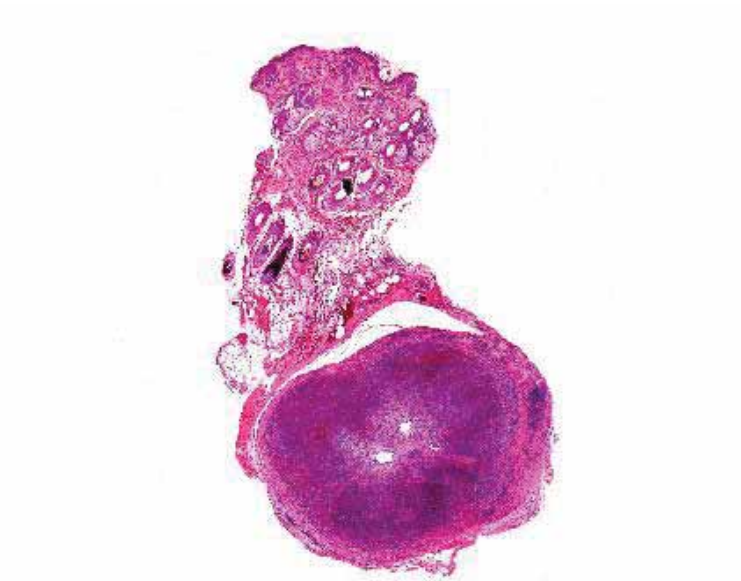
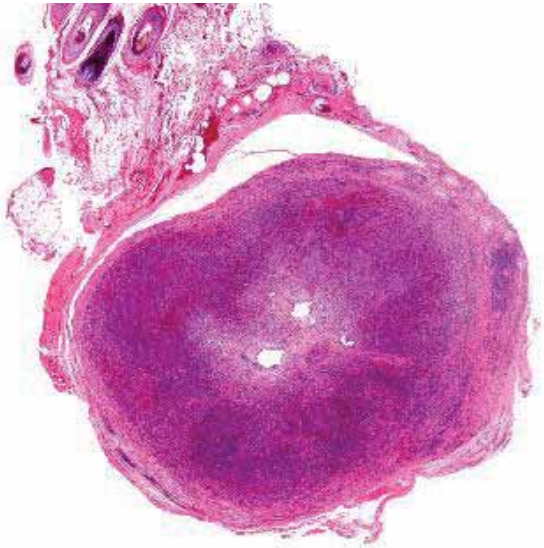
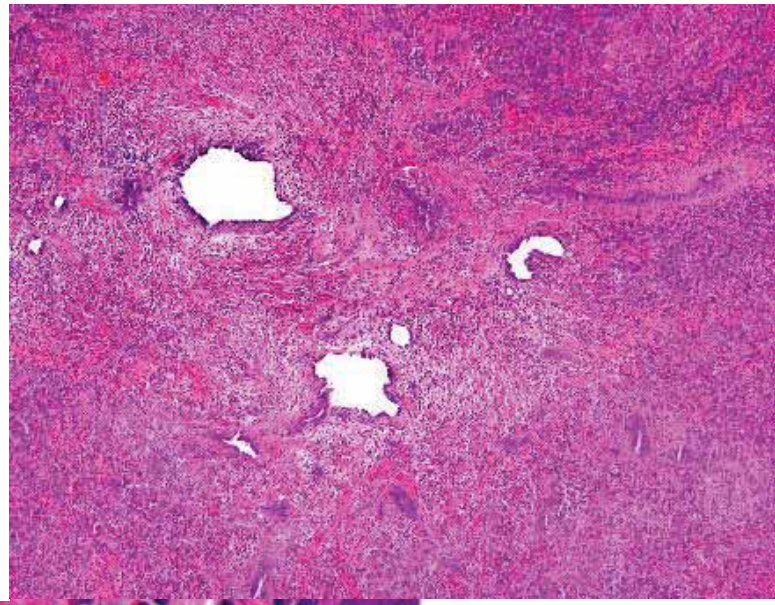
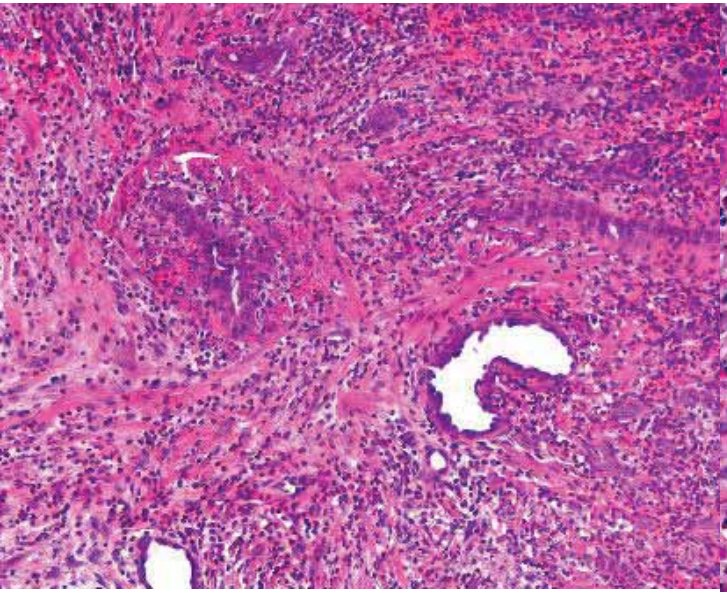
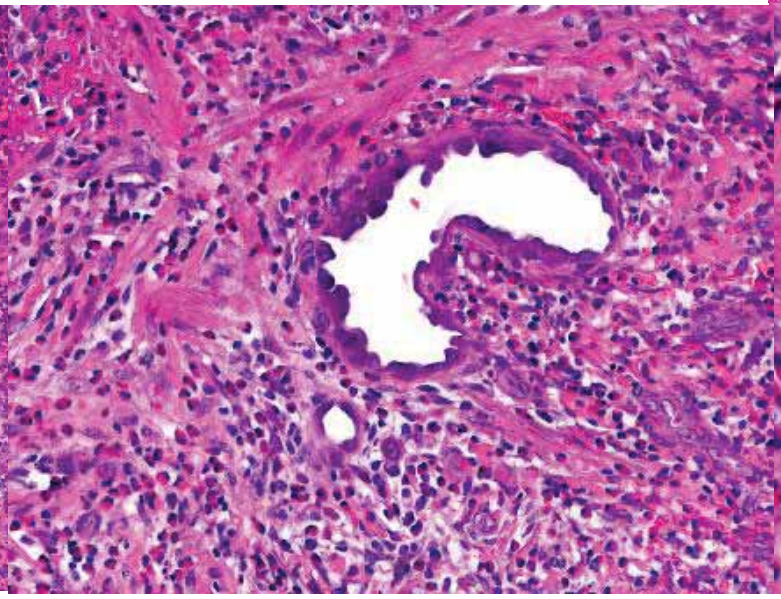
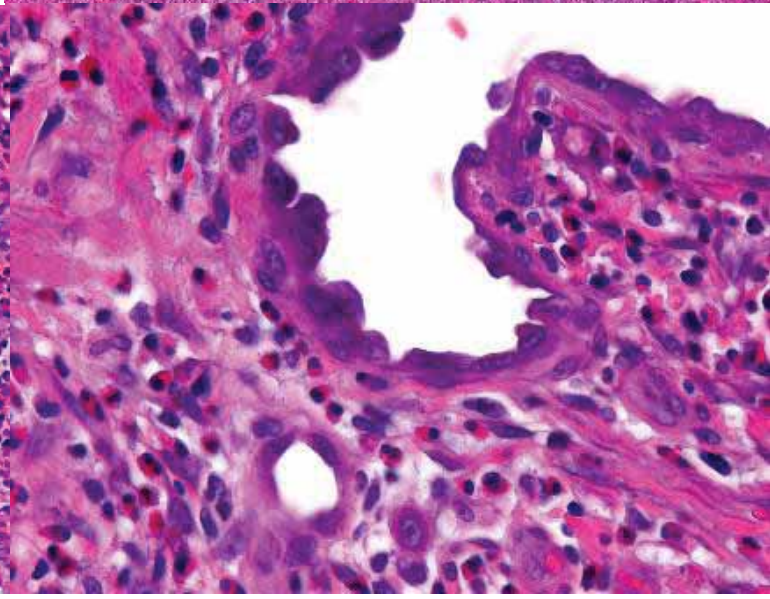

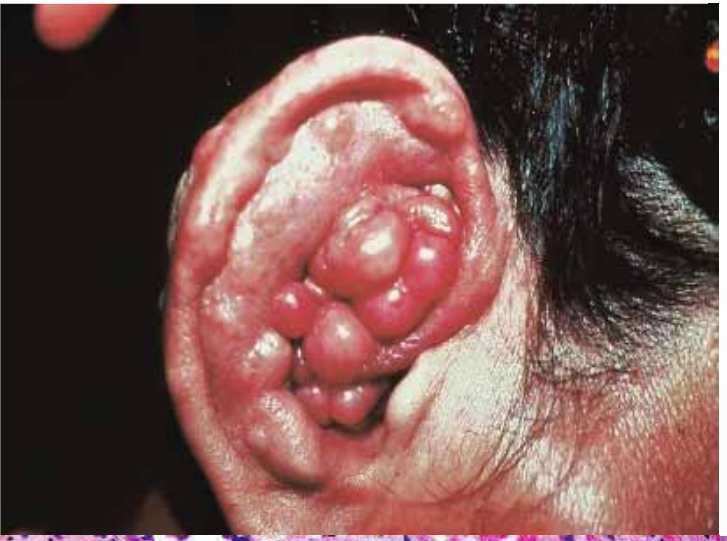

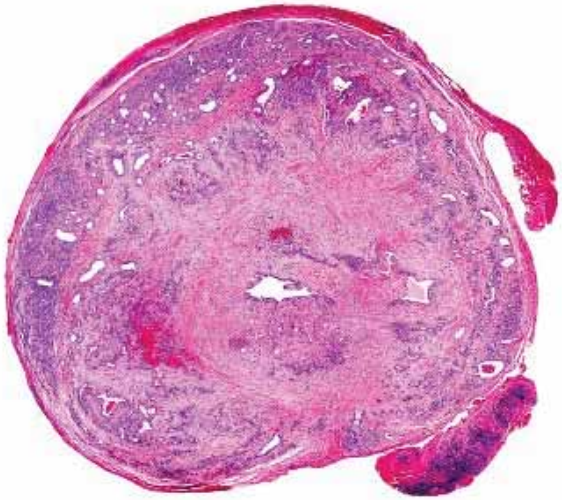

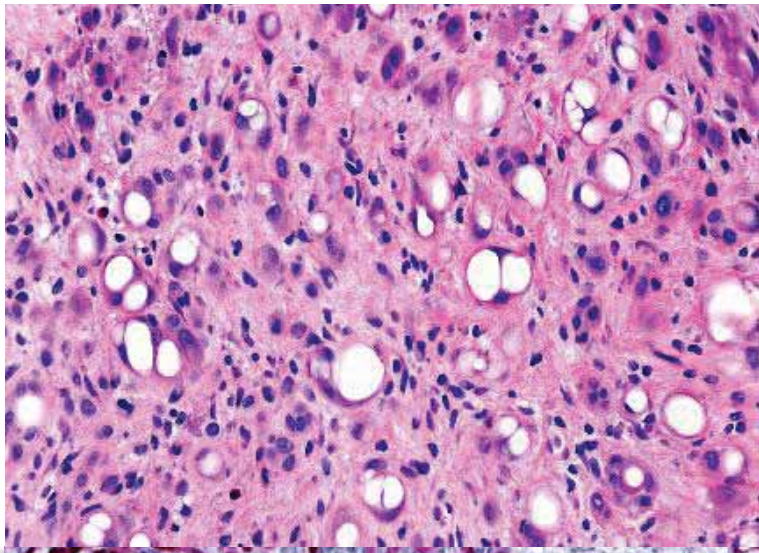

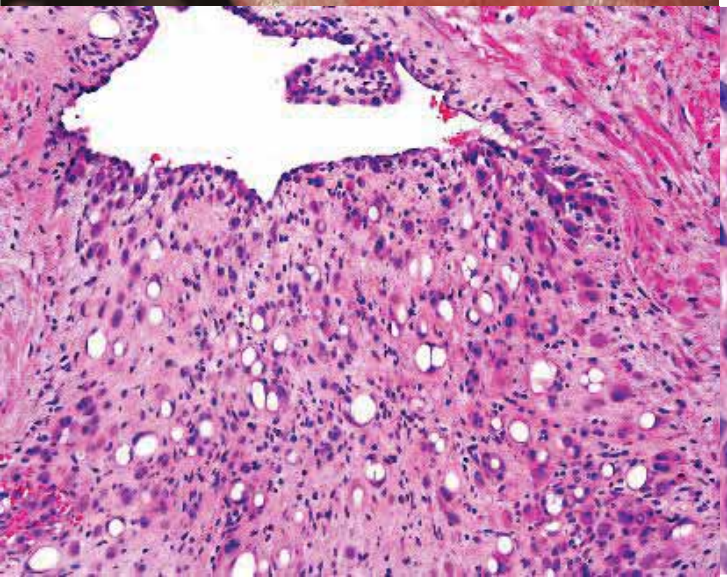

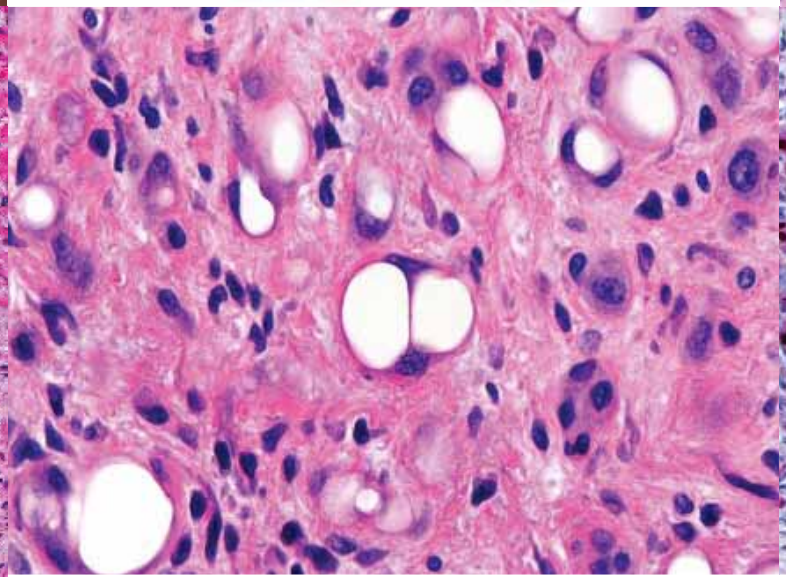

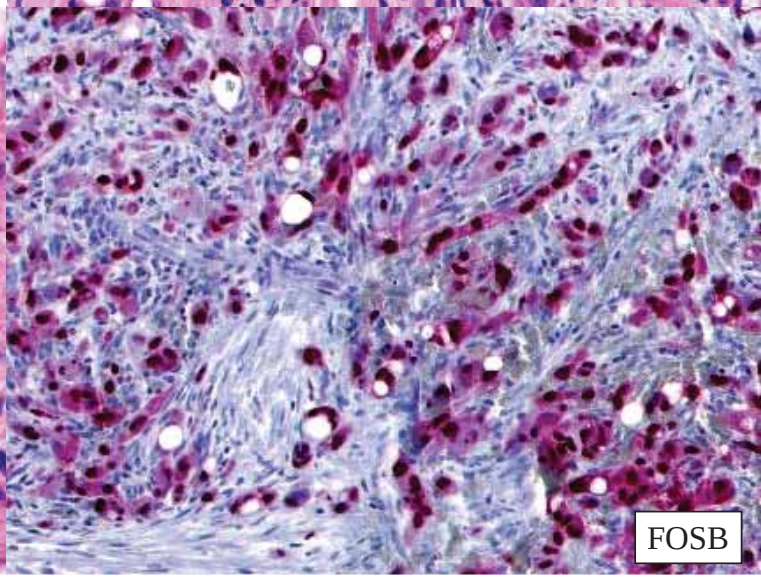
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SPECULATIONS
IN DERMATOPATHOLOGY

Richard J. Reed, Editor

Angiolymphoid hyperplasia with eosinophilia of the skin

Its nosological position in the spectrum of histiocytoid hemangioma

Juan Rosai, M.D.

I would like to express my views about an entity of relatively recent recognition that has gained a great deal of popularity in the dermatopathologic literature and that has generated some degree of controversy from its very inception.[1-6] This entity goes by a variety of names—some of these indirectly pointing to the differing and sometimes divergent views on its nature—but there is one that seems to have taken preference over the others, judging from the number of articles that boast it as part of their title. This name is "angiolymphoid hyperplasia with eosinophilia," and it is the one that will be used for the purposes of this discussion.

It is no accident that this term has become more popular than others; it lists in a relatively succinct fashion the most important morphologic features of the typical case, and it states that the process is reactive (hyperplastic) rather than neoplastic, thus reflecting the view of the majority of the writers who have dealt with the subject. There is general agreement as to how the typical case of this condition will present itself. In most instances, one or a few dermal nodules that have an "inflammatory appearance" on clinical inspection are found in the head and neck region of an adult, usually a middle-aged female. There is also a consensus as to what constitutes the typical microscopic appearance of the lesion: a noncapsulated dermal nodule with a central area of brisk vascular proliferation and eosinophilic infiltration, surrounded by a ring of mature lymphocytes, often forming lymphoid follicles with germinal centers. An additional microscopic feature of the disease that is mentioned with greater or lesser emphasis in the various accounts is the unusual appearance of the endothelial cells lining many of the proliferating vessels (Fig. 1). This endothelial cell has been variously described as "extraordinary," epithelial-like, representative of a hybrid between an endothelial cell and a histiocyte, and in several other fashions, all pointing to its unusual and perhaps unique features.

Other observations worthy of interest that have been made in the dermatopathologic literature about this disorder have been 1) the realization that cases with the same morphologic characteristics can occur in the deep subcutaneous tissues[7] (as a matter of fact, one of the earliest descriptions of this entity deals with cases located in the subcutis[2]) or in mucosal membranes[3,5]; 2) that these lesions, especially when subcutaneous, may be accompanied by

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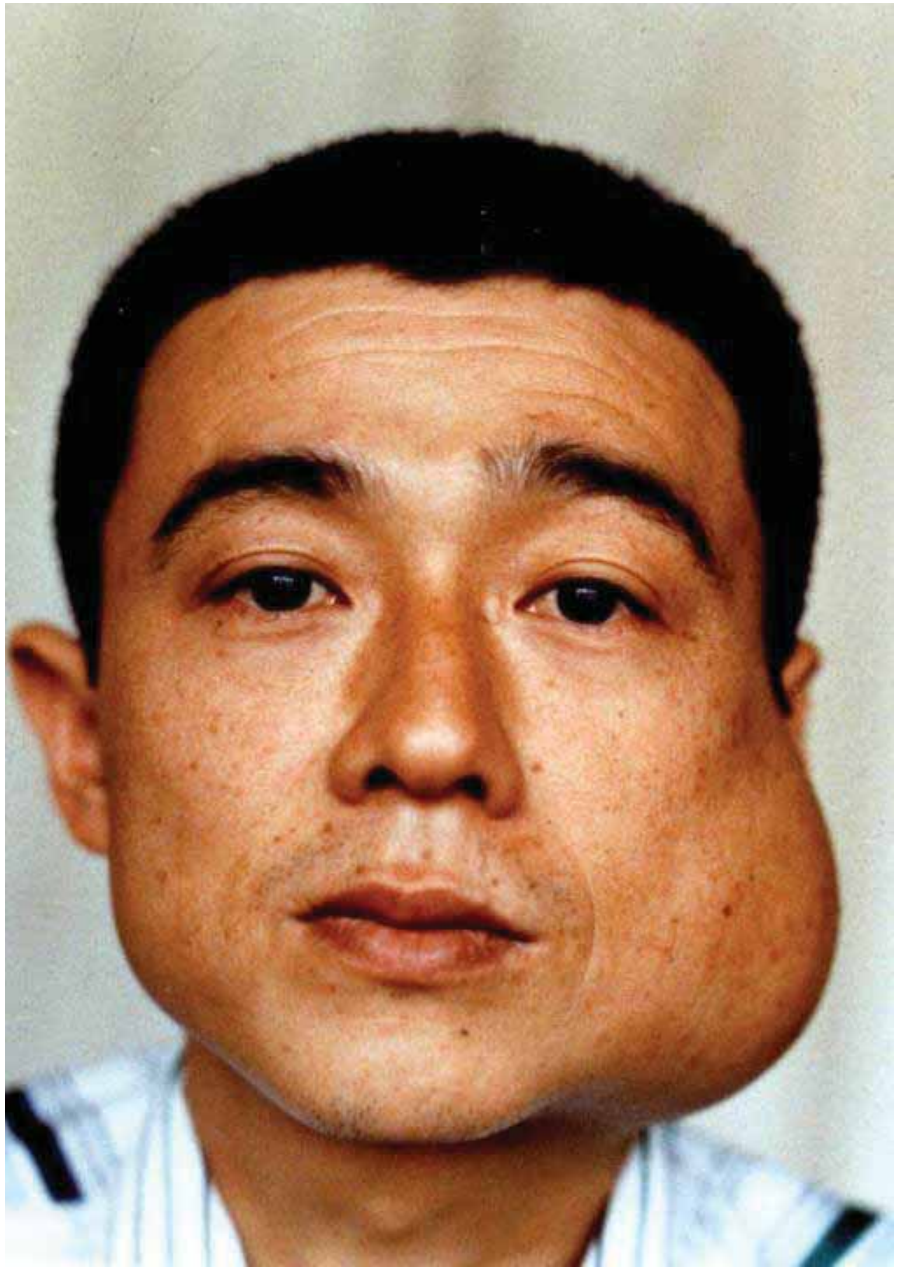
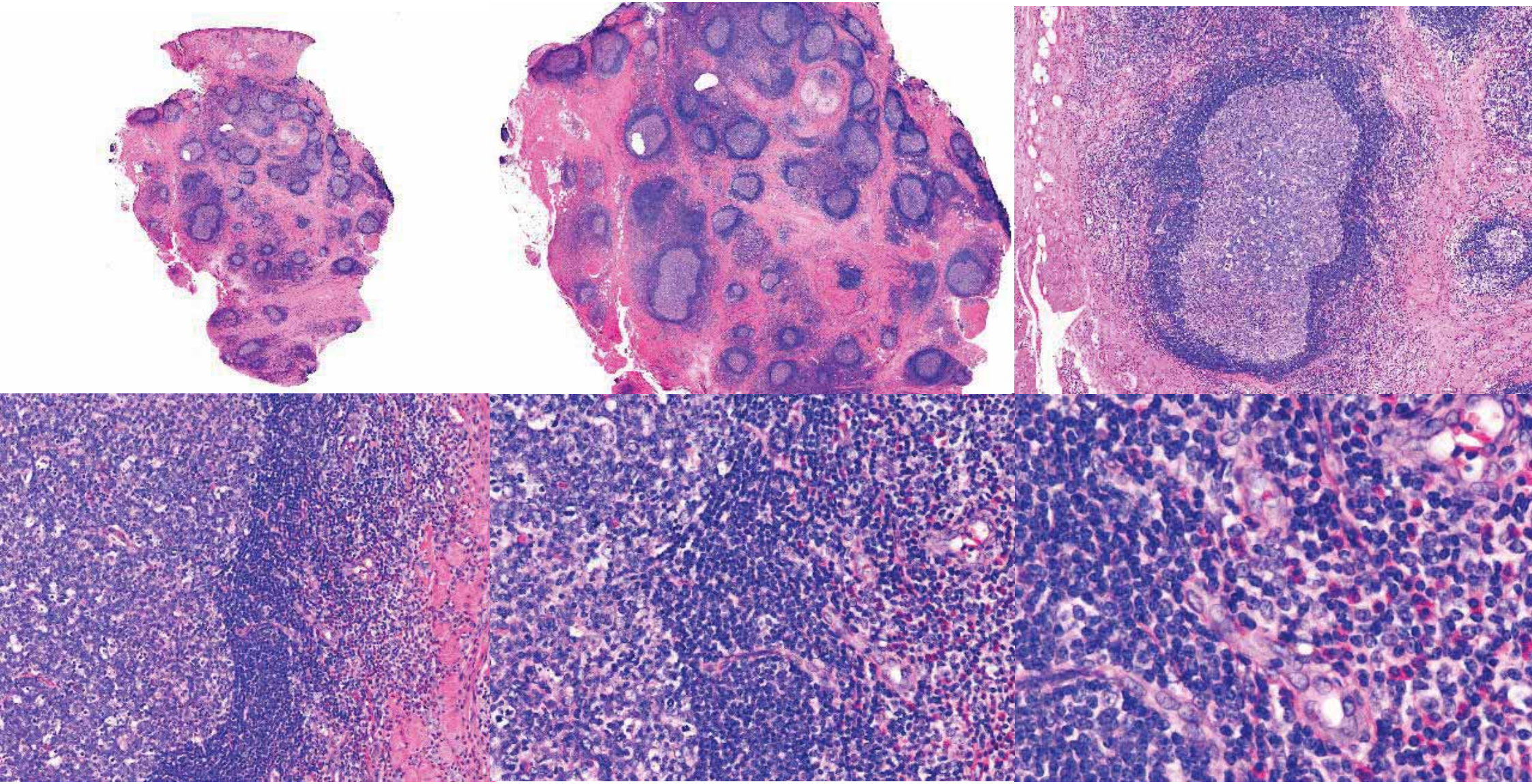
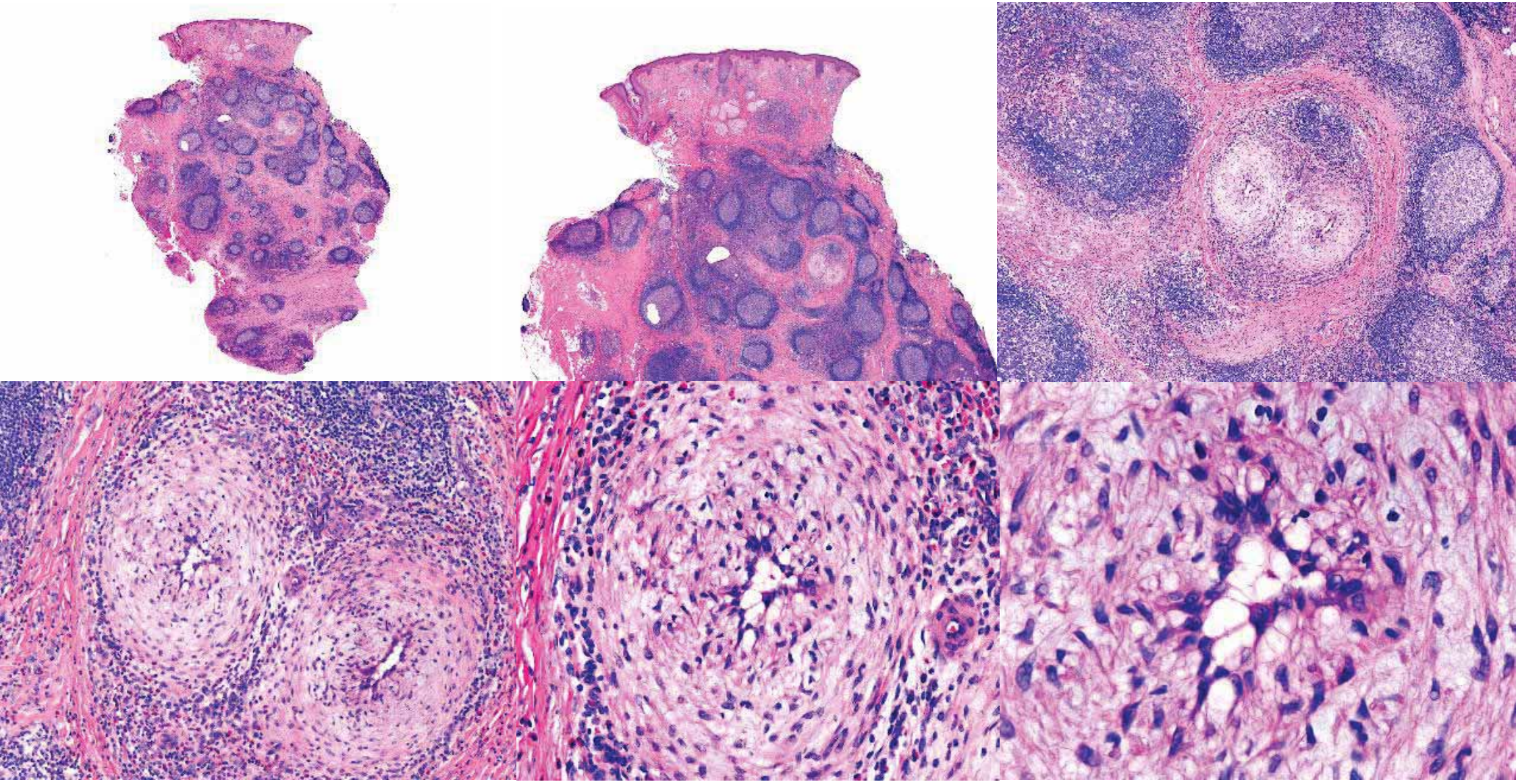
Not only is the vascular proliferation less prominent in the cases of Kimura's disease relative to the inflammatory component (as a matter of fact, it is hardly more pronounced than what one would expect in any inflammatory condition leading to luxuriant germinal center formation and tissue eosinophilia), but the characteristic endothelial cell that is such a constant feature of the cases of angiolymphoid hyperplasia with eosinophilia is largely absent.[14] Naturally, endothelial cells are plump in the vessels of Kimura's disease, and sometimes markedly so, as befits the cells of actively growing vessels. Yet, they lack the distinctive cytologic features of angiolymphoid hyperplasia.

In light of these observations, I must conclude that the alleged analogy between Kimura's disease and angiolymphoid hyperplasia with eosinophilia is spurious or at least unproved, and that the evidence on which it was based is inconclusive at best.







EOSINOPHILIC DERMATOSES

Eosinophil location	Clinical pattern	Disorder
Epidermis	Eczematous	Atopic dermatitis Contact dermatitis Cutaneous T cell lymphoma Hypereosinophilic syndrome with cutaneous manifestations Langerhans cell histiocytosis Scabies and larva migrans
Dermo-epidermal junction	Macular and papular	Drug eruption DRESS
Papillary dermis	Urticarial	Urticaria Eosinophilic cellulitis (Wells syndrome) Episodic angioedema with eosinophilia (Gleich syndrome) Polymorphic eruption of pregnancy
Subepidermal/papillary dermis and hair follicles	Blisters and pustules	Bullous pemphigoid Pemphigus Incontinentia pigmenti Eosinophilic pustular folliculitis Erythema toxicum neonatorum
Papillary and reticular dermis	Papular and nodular	Insect bite Prurigo nodularis Eosinophilic annular erythema Eosinophilic cellulitis (Wells syndrome) Angiolymphoid hyperplasia with eosinophilia and Kimura disease Eosinophilic dermatosis associated with hematologic malignancy Primary cutaneous CD30+ lymphoproliferative disorders
Subcutis	Panniculitic	Erythema nodosum Parasitic panniculitis
Superficial vascular dermal plexus	Vasculitic	Eosinophilic vasculitis Granuloma faciale Eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease)
Fascia	Fibrosis and sclerosis	Localized scleroderma Systemic sclerosis Eosinophilic fascitis

EOSINOPHILIC DERMATOSIS ASSOCIATED WITH HEMATOLOGIC MALIGNANCY

- Other names: exaggerated arthropod bite reactions, insect bite-like reactions and hematologic related malignancy-induced eosinophilic dermatosis.
- Recurrent episodes of pruritic papules, nodules, urticarial plaques or vesiculobullous eruption mostly involving the extremities.
- Histopathology: abundant perivascular lymphocytes and eosinophils in the superficial and deep dermis that extend to subcutaneous fat. No signs of vasculitis. Negative results of direct immunofluorescence studies for IgG, IgA, IgM and C3.
- Exclusion of other causes of tissue eosinophilia.
- Paraneoplastic disorder of unknown pathogenesis.

What's in a name? a new nomenclature has been proposed For *e*osinophilic *d*ermatosis of *h*ematologic *m*alignancy (EDHM): *h*ematologic-*r*elated *m*alignancy-*i*nduced *e*osinophilic *d*ermatosis (*He Remained*)

Philip R Cohen MD[1-4]

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Abstract

Hematologic-related malignancy-induced eosinophilic dermatosis (He Remained) has recently been introduced as a new nomenclature to describe the eosinophilic dermatosis that has previously been observed in patients with hematologic malignancies. The condition has been reported in 208 patients; the ratio of men to women is 1.3:1. It is most commonly observed in chronic lymphocytic leukemia patients (77%, 160/208 patients). The chronic and relapsing eosinophilic dermatosis typically presents with pruritic lesions that are pleomorphic in morphology and mimic other conditions. The definitive pathogenesis of *He Remained* is still being established. However, neoplastic leukemia B cells — directly or indirectly (by stimulating a reactive polyclonal T cell response) — likely have an etiologic role in the pathogenesis of this condition in chronic lymphocytic leukemia patients. In addition, recruitment of eosinophils to the skin may occur secondary to an immune shift toward a T helper 2 type response, possibly caused by the neoplastic cells, that results in these T cells producing interleukin 4. Clinical observations, currently based on the prompt (within four weeks) and sustained (at least 12 weeks to 6 months) resolution of *He Remained* in two elderly men with *He Remained*, suggests that dupilumab may be the treatment of choice in chronic lymphocytic leukemia patients with this condition.

Keywords: chronic, dermatosis, dupilumab, eosinophil, eosinophilic, he, hematologic, leukemia, lymphocytic, malignancy, remained

To the Editor:

I read with interest the excellent report by Almeida et al. [1] that described a 71-year-old man with a prior history of chronic lymphocytic leukemia — without need of treatment for approximately 13 years. He then presented with the new onset of both pancytopenia (indicating the progression of his leukemia to myelodysplastic syndrome) and a pruritic eruption consisting of multiple, erythematous and violaceous, papules and nodules on his face, ear helices, and neck. Correlation of his clinical history (neither medications nor insect bites), cutaneous lesion morphology, and pathology results (dilated capillaries with a superficial perivascular and interstitial mixed inflammatory infiltrate of neutrophils and numerous eosinophils) suggested the correct diagnosis. In addition, he had negative studies (including serologic testing for human immunodeficiency virus, syphilis, and hepatitis, skin biopsy for direct immunofluorescence and bullous pemphigoid antigen-1 and enzyme-linked immunosorbent assays for bullous pemphigoid antigen-2) that established a diagnosis of eosinophilic dermatosis of hematologic malignancy. He received symptomatic treatment for his skin condition with oral antihistamines; however, his condition rapidly deteriorated and he died. The authors emphasize that more effective treatment modalities for this condition need to be investigated [1].

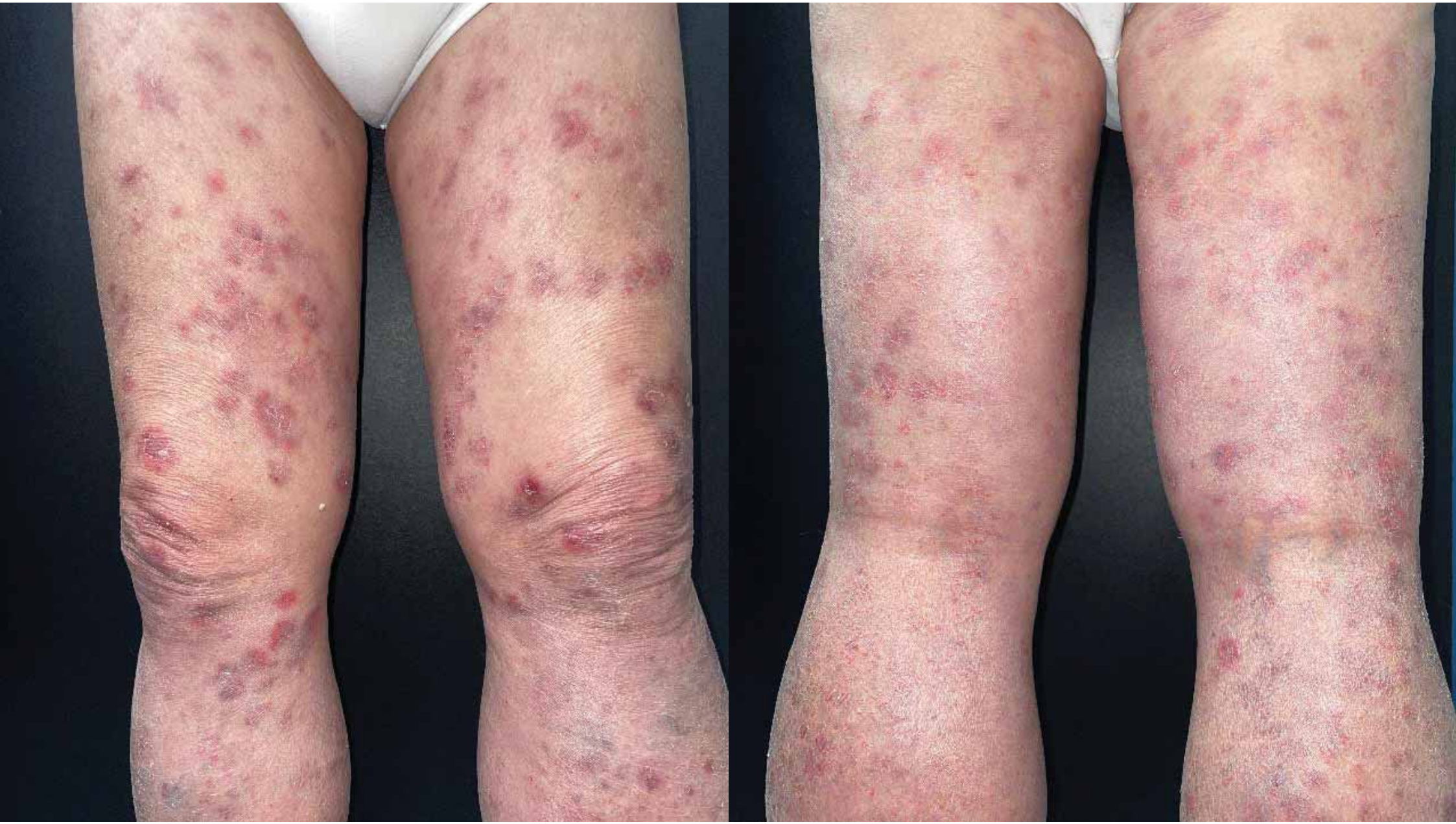
The term eosinophilic dermatosis of hematologic malignancy (EDHM) was proposed by Farber et al. [2] in 2012. However, the condition was originally

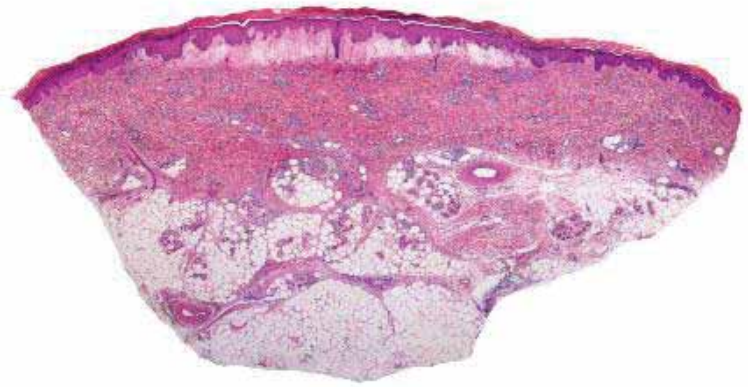
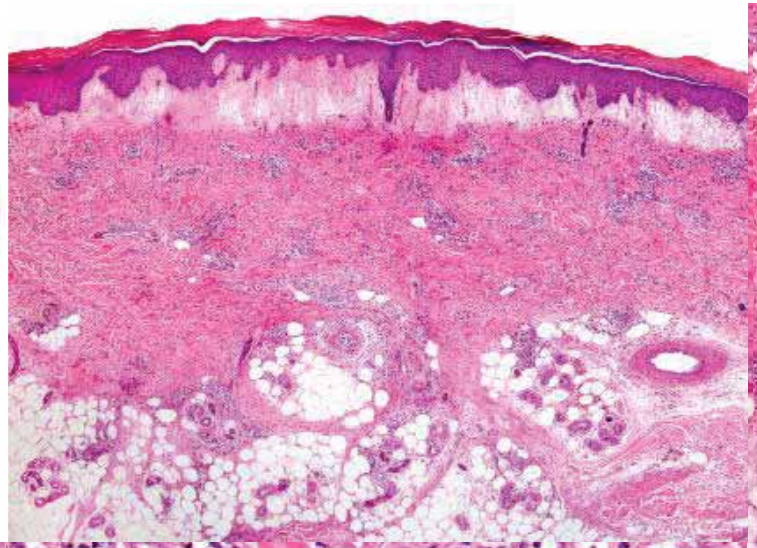
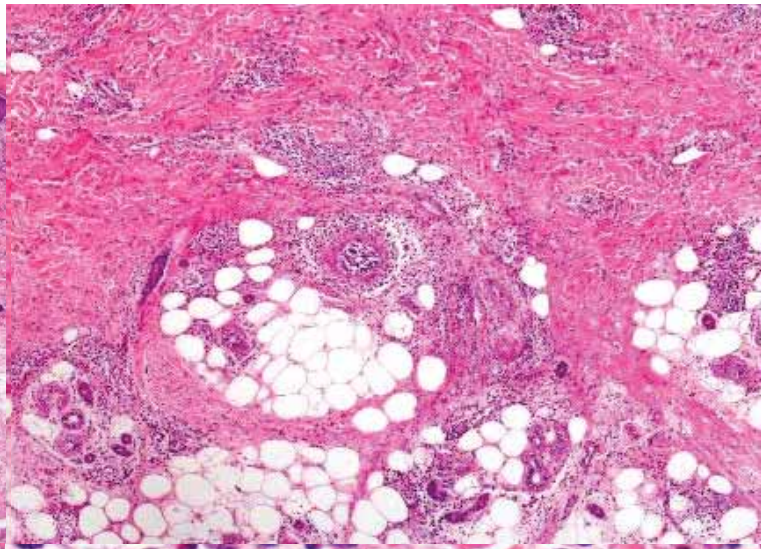
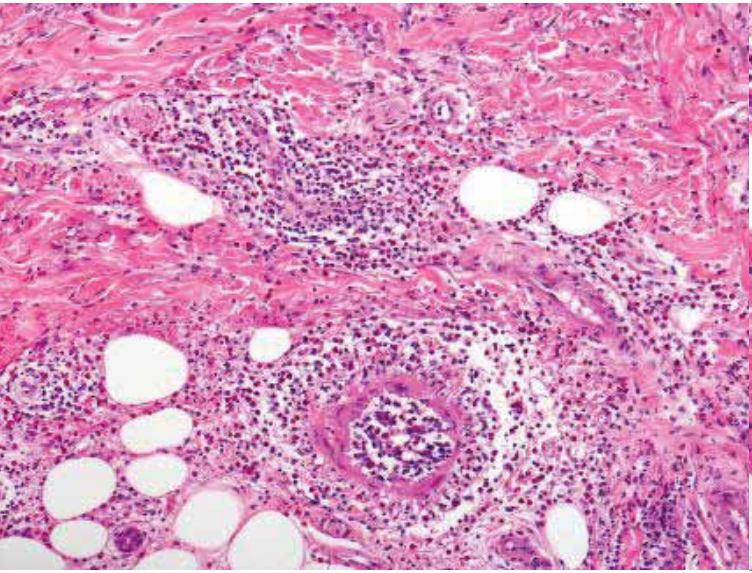
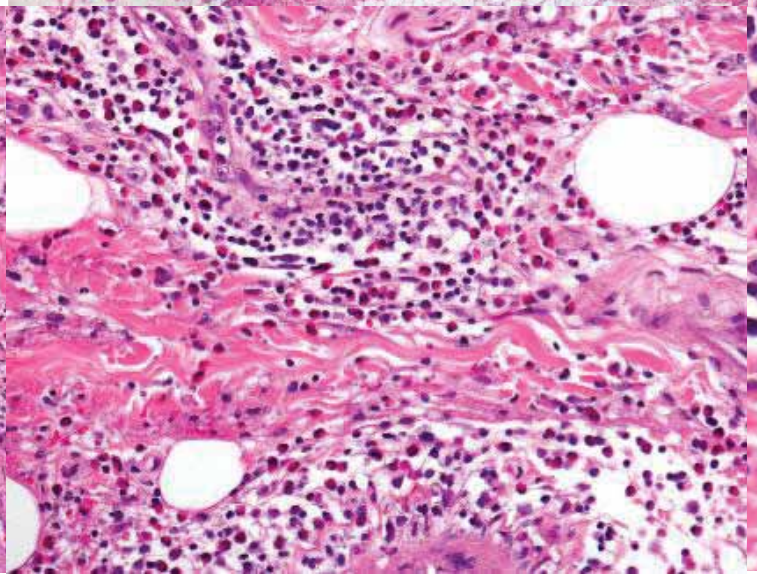
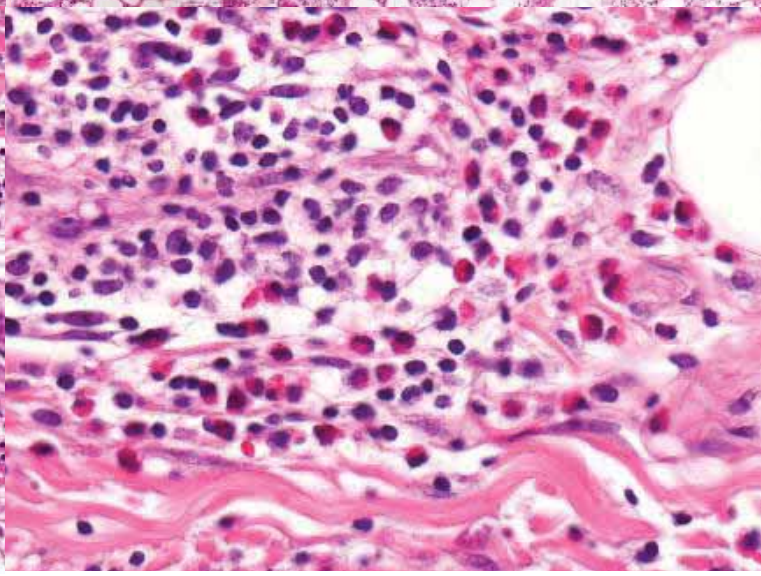
Table 1. *Nomenclature of the condition observed in patients with a hematologic malignancy whose cutaneous lesions had eosinophils in the dermis.*

Author (Year of publication)	Nomenclature	Reference
Weed (1965)	Exaggerated delayed hypersensitivity to mosquito bite in chronic lymphocytic leukemia	[3]
Barzilai et al. (1994)	Insect bite-like reaction in patients with hematologic malignant neoplasm	[4]
Byrd et al. (2001)	Eosinophilic dermatosis of myeloproliferative disease	[5]
Farber et al. (2012)	Eosinophilic dermatosis of hematologic malignancy	[2]
Visseaux et al. (2018)	T-cell papulosis associated with B-cell malignancy: TCP-BCM	[6]
Cohen (2020)	Hematologic-related malignancy-induced eosinophilic dermatosis: He Remained	[7]

Table 2. *Hematologic malignancies in patients with disease-related eosinophilic dermatosis.*

Malignancy	Number of patients	Percent of patients
Chronic lymphocytic leukemia	160	77.0
Lymphomas[a]	34	17.0
Other leukemias[b]	7	3.5
Other hematologic disorders[c]	5	2.5
Total	208	100.0



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WILEY JCP

ORIGINAL ARTICLE

Eosinophilic dermatosis of hematologic malignancy: Correlation of molecular characteristics of skin lesions and extracutaneous manifestations of hematologic malignancy

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Background: Skin diseases are frequent in patients with chronic lymphocytic leukemia (CLL) and other hematological neoplasias. Eosinophilic dermatosis (ED) of hematologic malignancy has long been considered a nonspecific cutaneous reaction pattern. Recently neoplastic cells have been shown to be present in ED, thus challenging the classification as a nonspecific dermatosis.
Methods: We report five patients with ED in association with CLL. We further investigated the presence of neoplastic B-cells in the skin infiltrate by immunohistochemistry and immunoglobulin heavy chain rearrangement and compared these to extracutaneous manifestations of CLL.
Results: The phenotype of the lymphocytic infiltrate was predominately CD3− (range: 60%-90%). CD20− and CD79a+ lymphocytes were less frequent, accounting for up to 15% (range: absent - 15%). CD23+ lymphocytes represented up to 20% (range: absent - 20%) of the infiltrate. The analysis of the immunoglobulin heavy chain rearrangement in the skin specimens showed clonal rearrangements in 4/5 patients and in three of these four patients clones were identical to extracutaneous CLL manifestations.
Conclusion: Our data show that neoplastic B-cells are very frequently found in ED when systematically evaluated. This findings support the hypothesis that leukemic cells play a pathogenetic role in ED of hematologic malignancy.

KEYWORDS
chronic lymphocytic leukemia, eosinophilic dermatosis of hematologic malignancy, immunoglobulin gene rearrangement, insect bite-like reaction, molecular genetics

1 | INTRODUCTION

Skin diseases are frequently reported in patients with chronic lymphocytic leukemia (CLL) and other hematological neoplasias.[1–4] Approximately 8% of all patients with CLL develop specific leukemic skin infiltrates, while a greater proportion of patients (25%-50%) suffer from nonspecific or paraneoplastic dermatoses without evidence of leukemic cells in the infiltrate.[1,2] Eosinophilic dermatosis (ED) of hematologic malignancy (synonym: insect bite-like reaction) has long been considered a rare and unique variant of a nonspecific cutaneous reaction pattern.[5–7] It was assumed that the underlying hematological disease causes an altered immune response and an increased secretion of TH2-cytokines (IL4 and IL5) stimulating the development of eosinophilic skin infiltrates.[8–12] ED in hematologic malignancy was first described by Weed.[13] Diagnostic criteria were defined by Byrd et al[6] and are based on clinical (insect bite-like eruption, refractory to standard therapies) and histological (superficial and deep lymphohistiocytic infiltrate with abundant eosinophils) criteria as well as on the patients' medical history (underlying hematological disease, exclusion of other reasons for tissue eosinophilia). Until 2012, approximately 40 to 50 cases of ED had been published in case reports and small case series.[14] Barrey et al[15] reported 48 patients with ED in a cohort of CLL patients in a retrospective study of the Israeli CLL Study Group. According to this study, the prevalence of ED in CLL patients is 6% to 7%, which is in line with other reports.[1,11] Thus ED occurs more often than previously assumed.[6,14]

Conclusion: Our data show that neoplastic B-cells are very frequently found in ED when systematically evaluated. This findings support the hypothesis that leukemic cells play a pathogenetic role in ED of hematologic malignancy.

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MÉMOIRE ORIGINAL

Dermatose éosinophilique associée aux hémopathies : étude clinique, histopathologique et immunohistochimique de six cas

Eosinophilic dermatosis associated with haematological disorders: A clinical, histopathological and immunohistochemical study of six observations

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Reçu le 8 septembre 2009 ; accepté le 2 février 2010

MOTS CLÉS
Dermatose éosinophilique associée aux hémopathies ;
Leucémie lymphoïde chronique ;
Lymphome du manteau ;
Piqûres d'insectes

Résumé
Introduction. — La dermatose éosinophilique associée aux hémopathies (DEH), anciennement appelée réaction exagérée aux piqûres d'insectes, est une dermatose prurigineuse observée le plus souvent au cours de la leucémie lymphoïde chronique (LLC). Nous en décrivons six observations associées à diverses hémopathies.
Malades et méthodes. — Nous avons étudié rétrospectivement les dossiers des malades de notre centre atteints de DEH entre 2004 et 2009, avec relecture des lames histologiques.
Résultats. — La moyenne d'âge au moment de l'éruption était de 75,6 ans. Trois malades étaient porteurs d'une LLC, deux d'un lymphome du manteau (LM), un d'un lymphome de type *mucosa associated lymphoid tissue* (MALT). L'éruption était très polymorphe, faite de papules et de plaques érythémateuses, urticariennes et prurigineuses, contemporaine ou postérieure au diagnostic de l'hémopathie. Elle précédait une récidive de l'hémopathie chez trois malades. La biopsie cutanée révélait un infiltrat dermique dense constitué de lymphocytes T CD4+ et d'éosinophiles. Trois cas présentaient l'originalité d'un infiltrat lymphocytaire T dense dans l'épithélium des follicules pileux, imitant un lymphome T pilotrope. Dans la majorité des cas, la DEH disparaissait après une chimiothérapie adaptée de l'hémopathie.

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Discussion. — Notre série montre que la présentation clinique de la DEH est polymorphe. L'apparition d'une DEH doit faire craindre la rechute d'une hémopathie B connue, voire inciter à la rechercher. Le traitement le plus efficace de cette dermatose semble être le traitement de l'hémopathie par une chimiothérapie adaptée. Le mécanisme pourrait être celui d'une réaction d'hypersensibilité médiée par une population T-helper 2 (Th2) réactionnelle à l'hémopathie B, entraînant une libération de cytokines dont l'interleukine (IL)-5, à l'origine d'une éosinophilie tissulaire.

EOSINOPHILIC DERMATOSES

Eosinophil location	Clinical pattern	Disorder
Epidermis	Eczematous	Atopic dermatitis Contact dermatitis Cutaneous T cell lymphoma Hypereosinophilic syndrome with cutaneous manifestations Langerhans cell histiocytosis Scabies and larva migrans
Dermo-epidermal junction	Macular and papular	Drug eruption DRESS
Papillary dermis	Urticarial	Urticaria Eosinophilic cellulitis (Wells syndrome) Episodic angioedema with eosinophilia (Gleich syndrome) Polymorphic eruption of pregnancy
Subepidermal/papillary dermis and hair follicles	Blisters and pustules	Bullous pemphigoid Pemphigus Incontinentia pigmenti Eosinophilic pustular folliculitis Erythema toxicum neonatorum
Papillary and reticular dermis	Papular and nodular	Insect bite Prurigo nodularis Eosinophilic annular erythema Eosinophilic cellulitis (Wells syndrome) Angiolymphoid hyperplasia with eosinophilia and Kimura disease Eosinophilic dermatosis associated with hematologic malignancy Primary cutaneous CD30+ lymphoproliferative disorders
Subcutis	Panniculitic	Erythema nodosum Parasitic panniculitis
Superficial vascular dermal plexus	Vasculitic	Eosinophilic vasculitis Granuloma faciale Eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease)
Fascia	Fibrosis and sclerosis	Localized scleroderma Systemic sclerosis Eosinophilic fasciitis

Journal of Cutaneous Pathology 1986: **13**, 1–12

Eosinophilic panniculitis: a clinicopathologic study

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[1]Department of Dermatology and the [2]Division of Allergic Diseases and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA

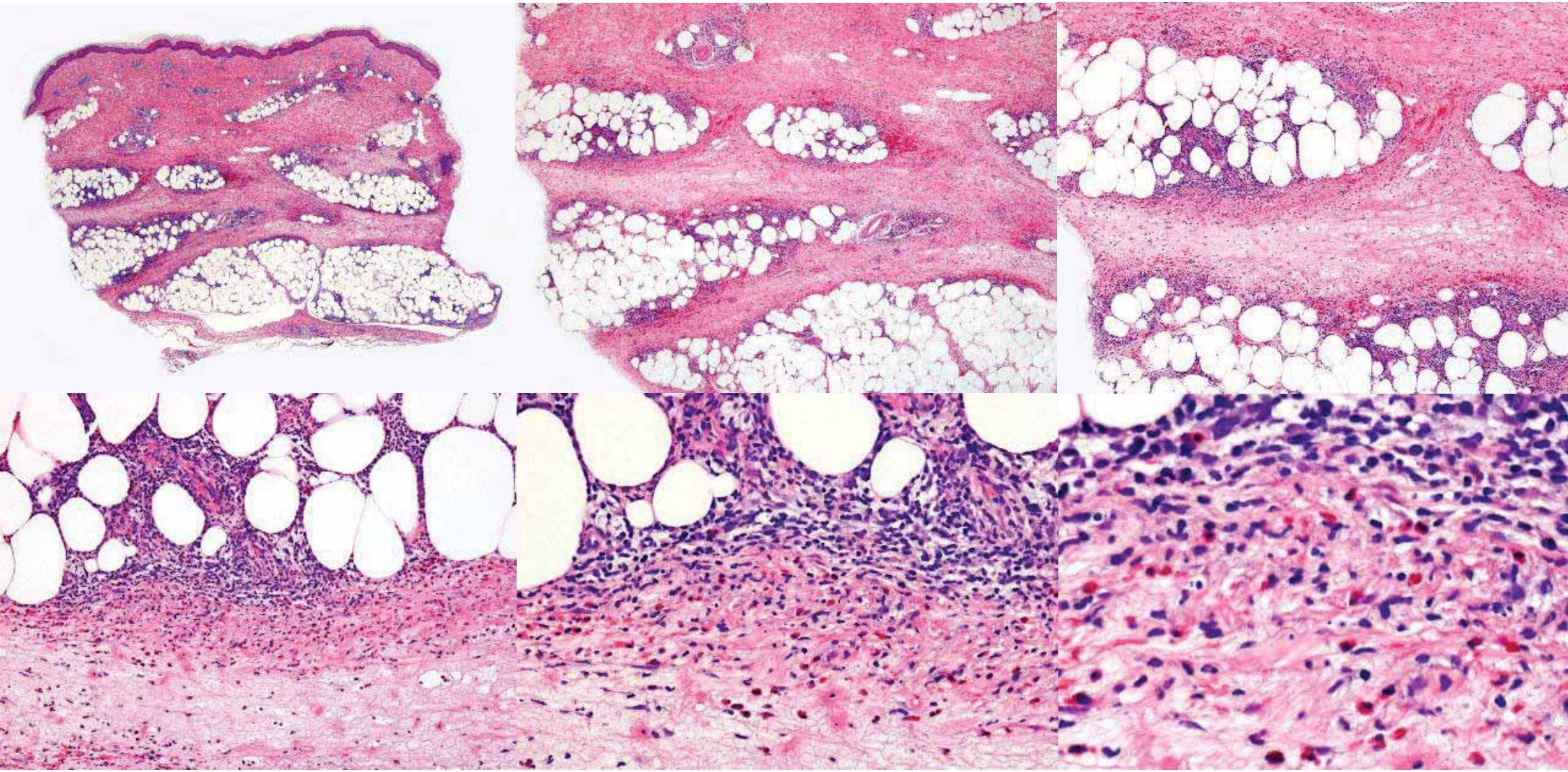
Study of 18 patients with biopsy diagnoses of eosinophilic panniculitis revealed diverse patterns of systemic disease, including Wells' syndrome, vasculitis, atopy, and erythema nodosum as well as localized panniculitis. Significant associated diseases included psychiatric illness, 6 (drug dependency, 4); atopy, 5 (asthma, 3); malignancies, 5; immune complex vasculitis, 4; thyroid disease, 2; Wells' eosinophilic cellulitis, 2; glomerulonephritis and sarcoidosis, 1 each. The skin lesions varied from urticarial papules and plaques to purpura, pustules, and ulcerative lesions but always included a nodular subcutaneous component, frequently as a presenting complaint. Eosinophilic panniculitis is a non-specific finding that can signify localized disease, such as an insect bite or injection lipophagic granuloma in a drug-dependent patient, or systemic lymphoma or immune reactive disease. Eosinophilic panniculitis in erythema nodosum is perhaps its most confusing presentation.

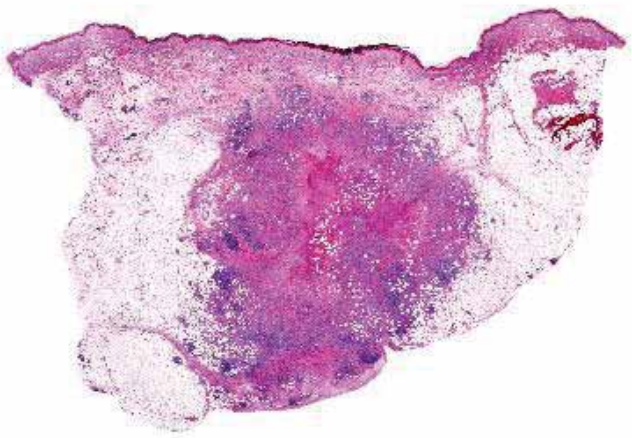
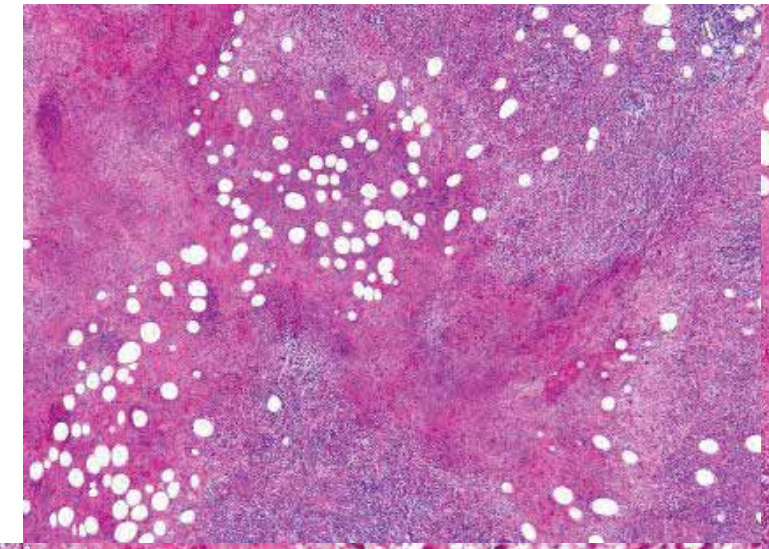
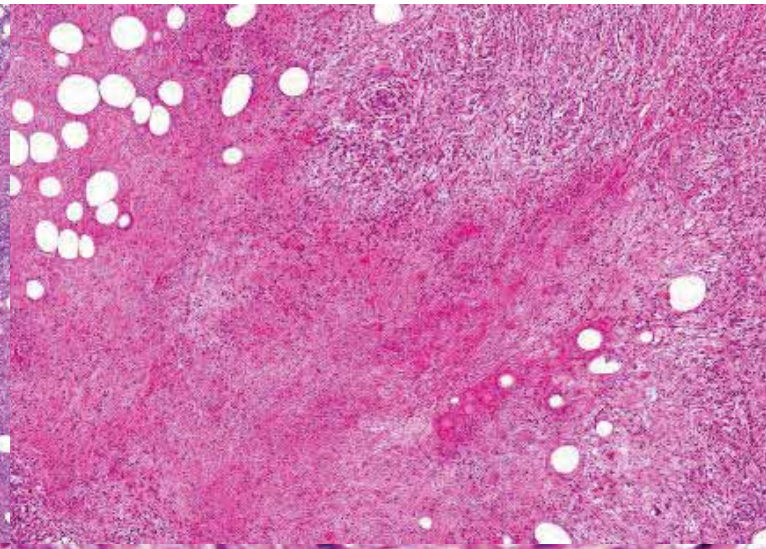
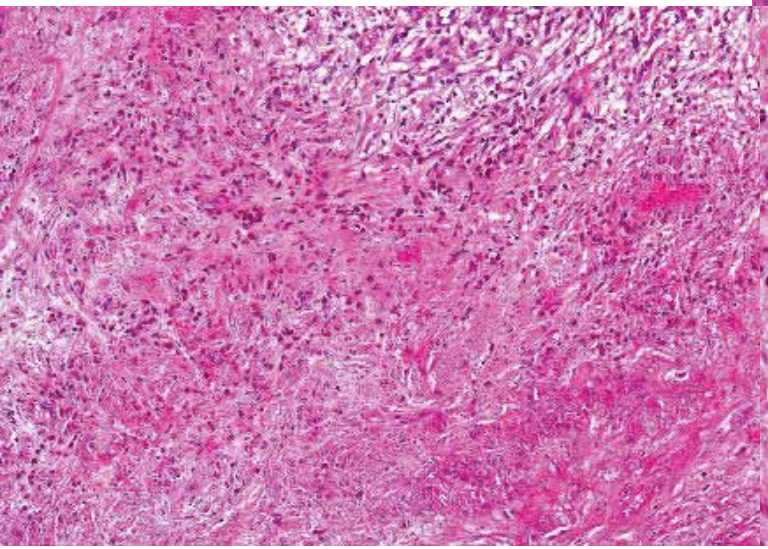
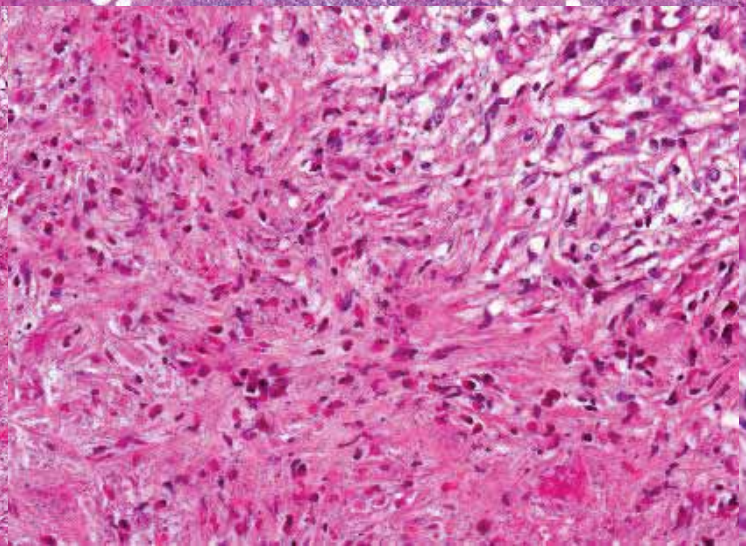
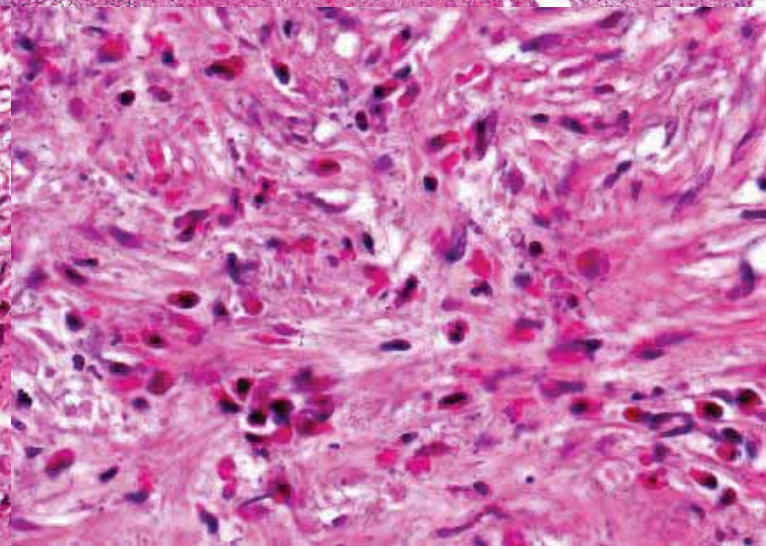
Accepted for publication July 2, 1985

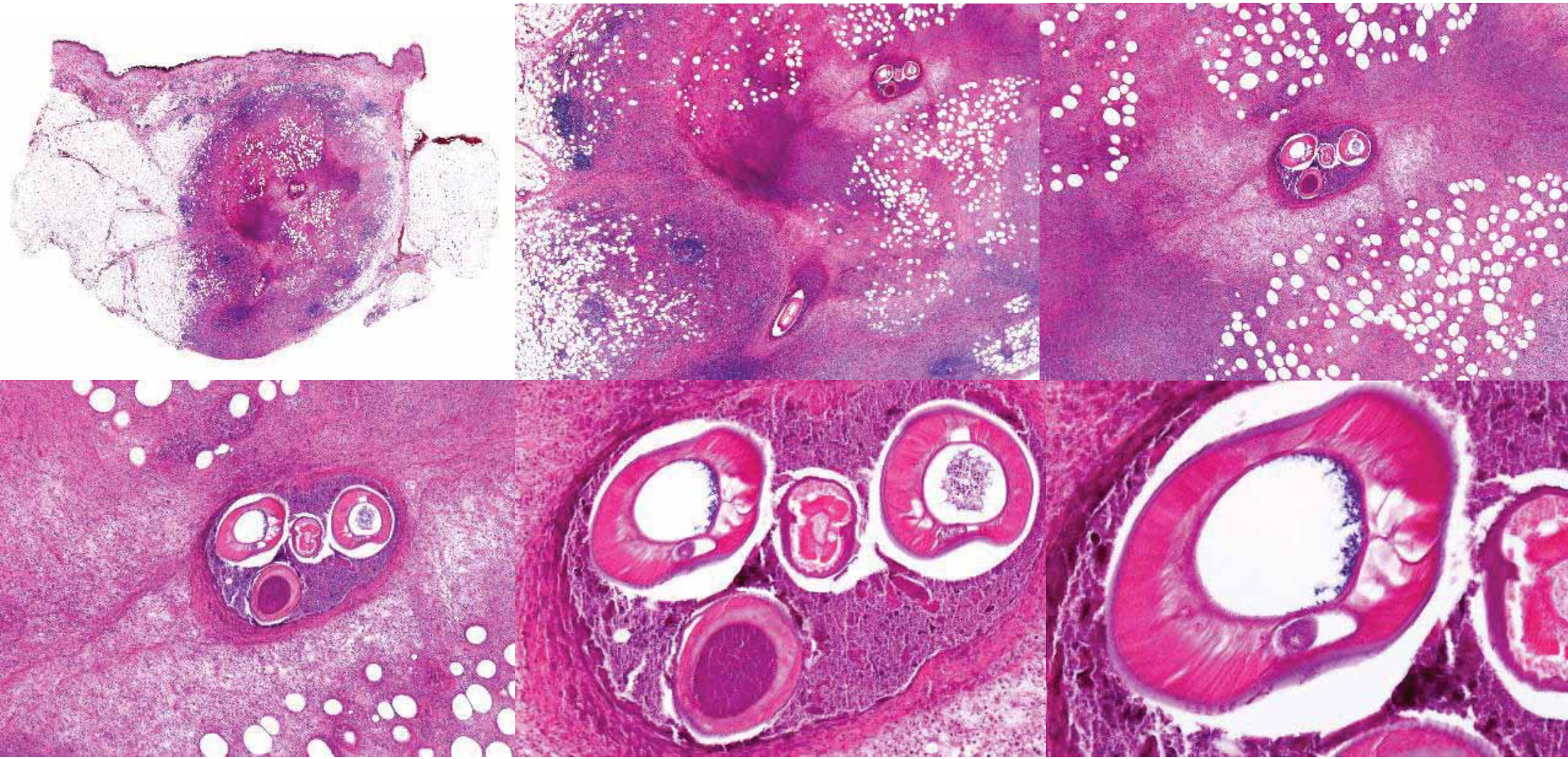
EOSINOPHILIC PANNICULITIS

Septal or lobular panniculitis with numerous eosinophils in the infiltrate. It is not a specific entity, but a histopathologic pattern seen in:

- Wells syndrome
- Erythema nodosum
- Vasculitis
- Parasitic infections
- Malignant lymphomas
- Atopy
- Narcotic dependence with injection granulomas
- Deep larva migrans





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Fascia	Fibrosis and sclerosis	Localized scleroderma Systemic sclerosis Eosinophilic fasciitis

EOSINOPHILIC VASCULITIS

- Cutaneous necrotizing vasculitis with predominantly eosinophilic infiltrate in the vessels wall:
  1. Eosinophilic vasculitis associated with connective tissue disease.
  2. Eosinophilic vasculitis in eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease).
  3. Recurrent cutaneous eosinophilic vasculitis.

Eosinophilic vasculitis in connective tissue disease

Ko-Ron Chen, MD,[a] W. P. Daniel Su, MD,[a] Mark R. Pittelkow, MD,[a] Doyt L. Conn, MD,[b] Terry George, BS,[b] and Kristin M. Leiferman, MD[a] *Rochester, Minnesota*

Background: Neutrophilic and lymphocytic vascular inflammation is common in vasculitis associated with connective tissue disease (CTD). We recently identified eight patients with CTD and eosinophilic vasculitis.

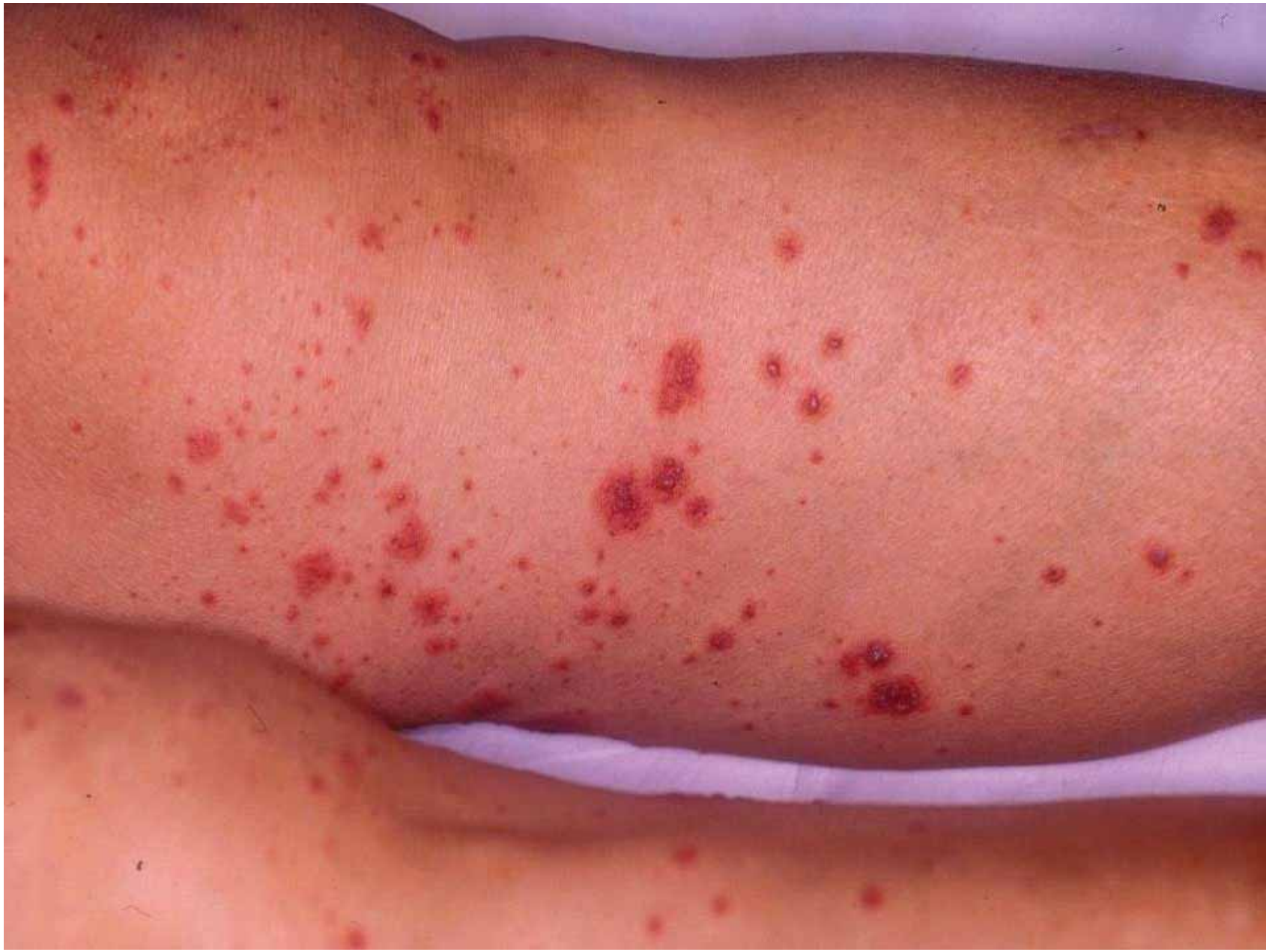
Objective: The purpose of this study was to characterize a variant form of vasculitis in CTD with eosinophilic infiltration.

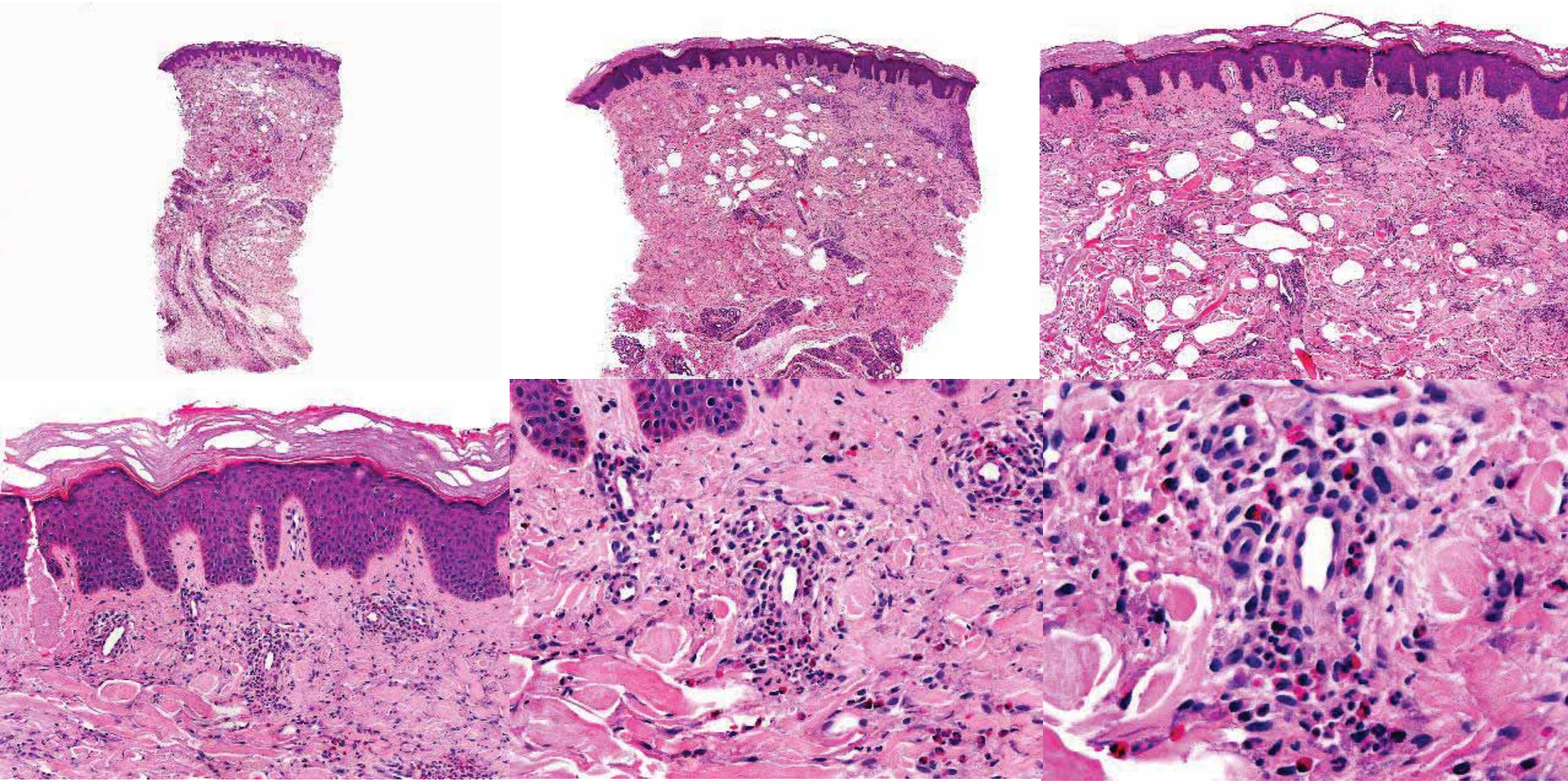
Methods: Of 98 CTD patients with cutaneous necrotizing vasculitis, eight were found with predominantly eosinophilic vascular infiltration. Nine CTD patients with cutaneous neutrophilic vasculitis were identified for comparison. Clinical and laboratory findings were reviewed and compared. Indirect immunofluorescence for eosinophil granule major basic protein (MBP), neutrophil elastase, and mast cell tryptase was performed on lesional tissue. MBP levels and eosinophil survival enhancing activity were assayed in sera from three patients.

Results: The patients with eosinophilic vasculitis had depressed serum complement levels and peripheral blood eosinophilia; MBP levels were elevated in serum and eosinophil survival was prolonged. Immunofluorescence of tissue showed marked angiocentric eosinophil MBP staining with peripheral neutrophil elastase staining; mast cell tryptase staining was notably absent. The patients with neutrophilic vasculitis were variably hypocomplementemic and did not have peripheral blood eosinophilia. Immunofluorescence showed marked angiocentric neutrophil elastase staining with scattered eosinophil MBP staining; mast cell tryptase staining showed normal mast cell numbers.

Conclusion: Patients with eosinophilic vasculitis, CTD, and hypocomplementemia show vessel wall destruction in association with vessel wall deposition of cytotoxic eosinophil granule MBP, which suggests that eosinophils mediate vascular damage in this disease process. In addition, perivascular mast cells appear diminished, thereby suggesting that mast cell degranulation occurs.

(J Am Acad Dermatol 1996;35:173-82.)





ALLERGIC GRANULOMATOSIS, ALLERGIC ANGIITIS, AND PERIARTERITIS NODOSA *

JACOB CHURG, M.D., and LOTTE STRAUSS, M.D.
(From the Laboratories, Division of Pathology, the Mount Sinai Hospital, New York 29, N.Y.)

During the past 25 years a relation between allergic states and vascular lesions of the type seen in periarteritis nodosa has been firmly established by study of human disease and by experimental evidence. Gruber [1] suggested that periarteritis nodosa is a hyperergic vascular response to infection. Cohen, Kline, and Young [2] postulated a causal relationship between allergy, as exemplified by severe asthma, and periarteritis nodosa developing in its course. Wilson and Alexander,[3] on reviewing the literature, found association of these two diseases in 18 per cent of 300 cases of periarteritis nodosa. Cases of this type have been studied also by Rackemann and Greene,[4] who described the clinical syndrome in some detail, and by Harkavy,[5] who interpreted this syndrome as an expression of vascular allergy. Rich [6,7] and other authors [8] found vascular lesions in patients who developed reactions to foreign serum or drugs (sulfonamides, iodine, dilantin), which Rich believed to be identical with those of periarteritis nodosa. Rich and Gregory [9] were able to reproduce these lesions experimentally in animals.

While most of the authors concerned themselves with pathologic changes in the vascular system, there are a number of reports in the literature indicating that, in addition, widely dispersed extravascular lesions may occur in connective tissue (Rössle,[10] Bergstrand,[11] Rich,[12] Smith [13]). Such lesions are characterized by inflammatory exudate rich in eosinophilic leukocytes, by necrosis of the exudate, and by severe alteration of collagen with granulomatous (epithelioid and giant cell) reaction.

The present report deals with cases of severe asthma which presented the clinical syndrome described by Rackemann and Greene,[4] and by Harkavy,[5] and which, on pathologic examination, exhibited the granulomatous extravascular lesions noted above, as well as necrotizing, inflammatory, and granulomatous vascular changes.

Most of our material is derived from cases autopsied in the Department of Pathology of the Mount Sinai Hospital, New York City. Of 23 patients in whom death was accompanied, or preceded, by severe asthma (status asthmaticus), 9 showed a strikingly uniform clinical

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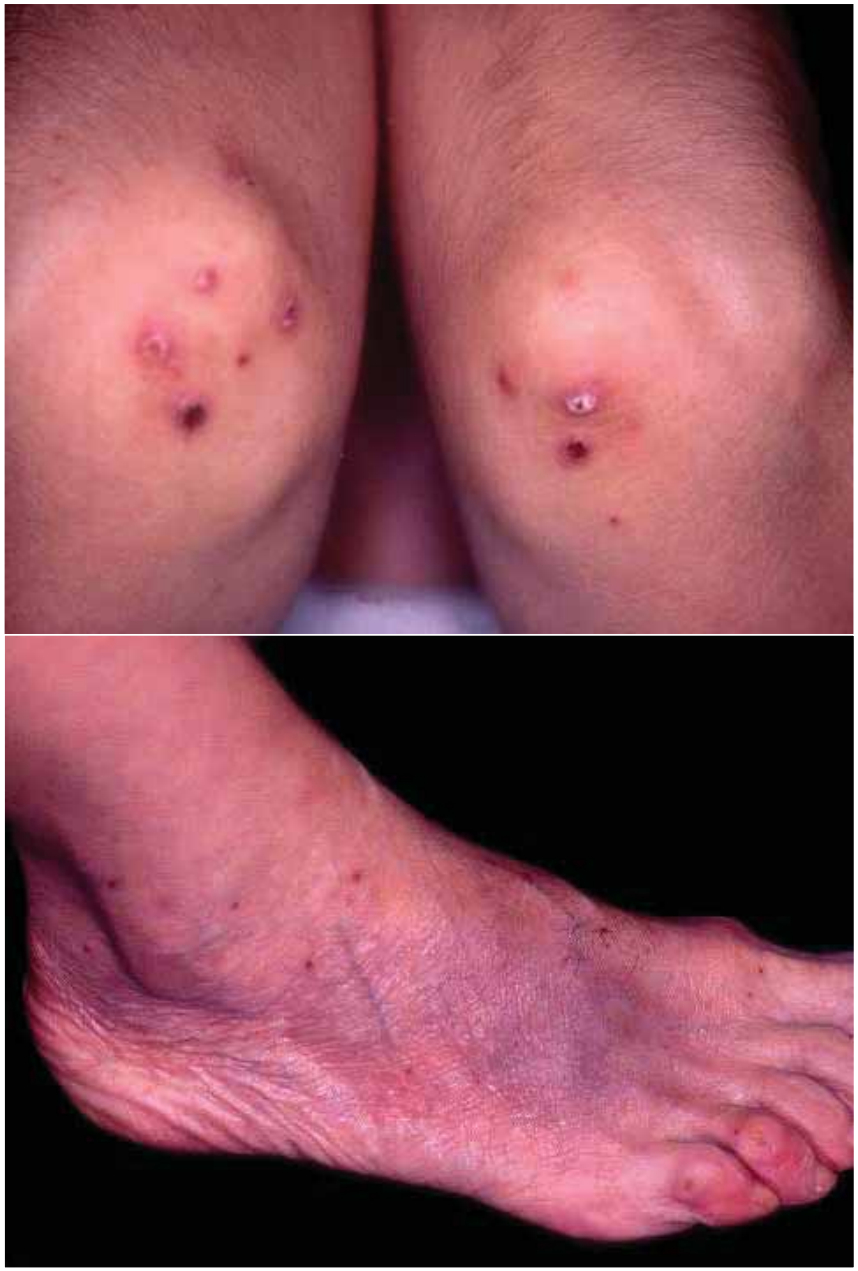
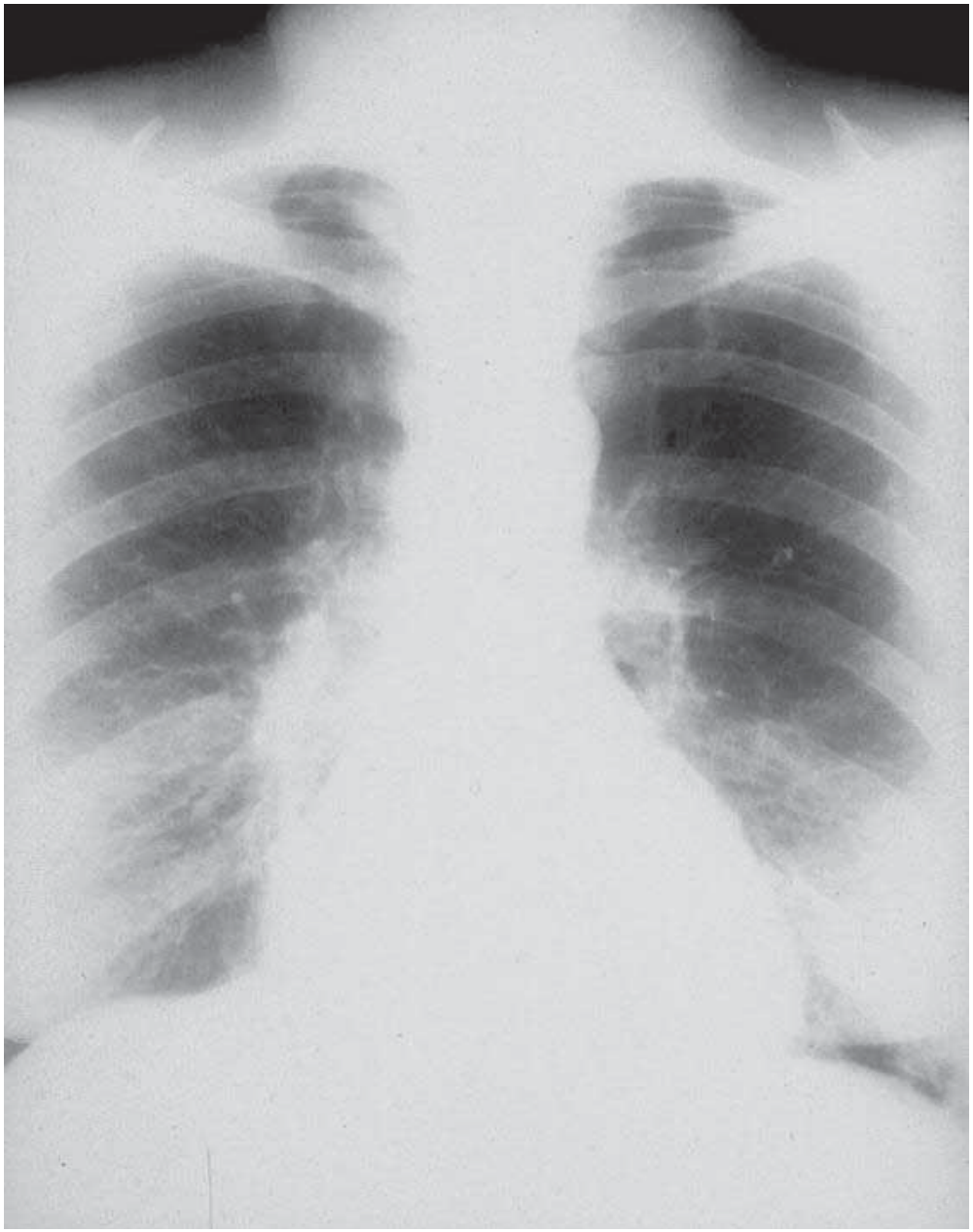
Am J Pathol 1951;27:277-301

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

(Churg-Strauss disease)

- Clinical features:
  - Pulmonary involvement (asthma).
  - Small vessels vasculitis.
  - Hypereosinophilia in blood and in tissues.
  - p-ANCA anti-myeloperoxidase antibodies.
- Cutaneous lesions:
  - Purpura: petechiae and ecchymosis.
  - Papules that tend to ulcerate and cover with crusts.
  - Subcutaneous nodules.
- Histopathology:
  - In purpuric lesions: leukocytoclastic vasculitis with numerous eosinophils.
  - In papules and subcutaneous nodules: extravascular necrotizing granuloma (Winkelmann or Churg-Strauss granuloma) with numerous eosinophils.





Cutaneous clinicopathologic correlation of allergic granulomatosis

Christopher P. Crotty, M.D., Richard A. DeRemee, M.D., and R. K. Winkelmann, M.D., Ph.D.
Rochester, MN

Allergic granulomatosis is a distinct clinical syndrome occurring in adults with asthma, eosinophilia, and multisystem vasculitis. Atopy and drug sensitivity are other important features. The skin reactions are most commonly nodular and inflammatory lesions. A unique feature is the deep papulonodules, which may occur singly on the scalp or symmetrically on the extremities. Cutaneous findings may range from purpura to urticaria and ulceration. The most common histologic finding is the extravascular granuloma; however, necrotizing vasculitis of small vessels is seen, as well as periarteritis nodosa involving larger vessels of the skin. This varied histologic and clinical spectrum seen in patients with systemic allergic granulomatosis is a reflection of a unique host response to multiple antigens. The cutaneous findings imply that allergic granulomatosis probably represents a unique host response to the same causative and pathogenetic factors as are usually found in periarteritis nodosa and necrotizing vasculitis. (J Am Acad Dermatol **5**:571-581, 1981.)

Cutaneous manifestations of Churg-Strauss syndrome: A clinicopathologic correlation

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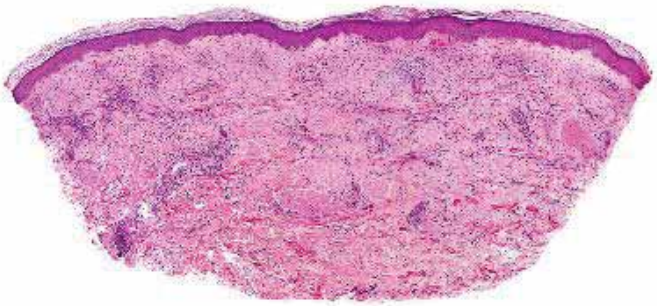
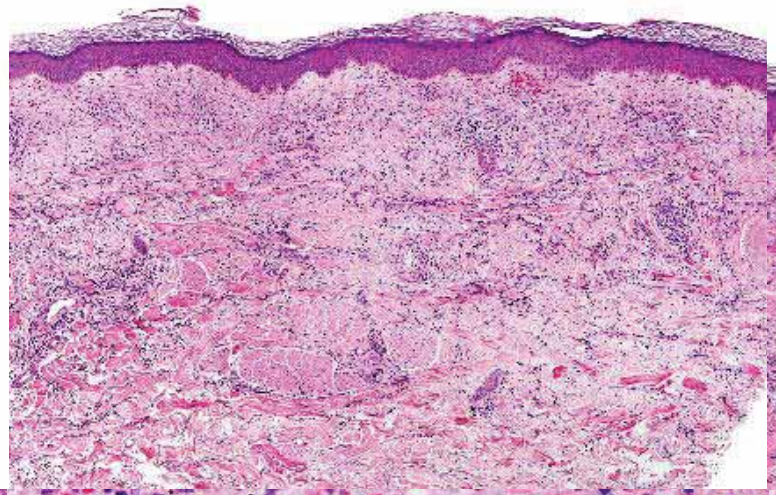
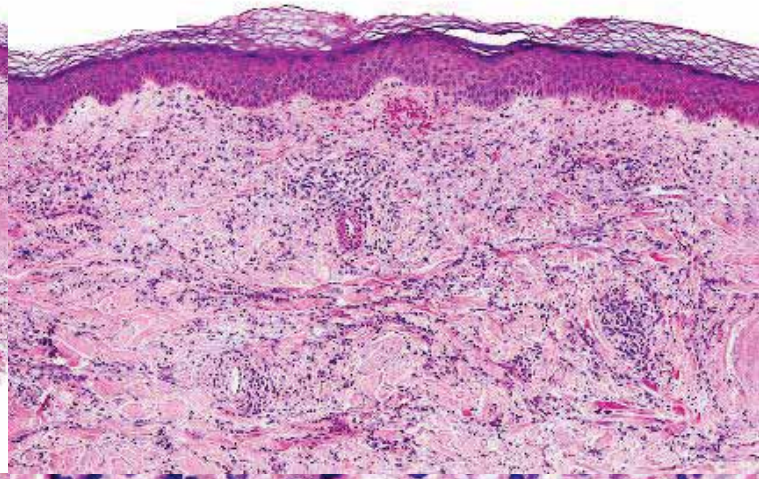
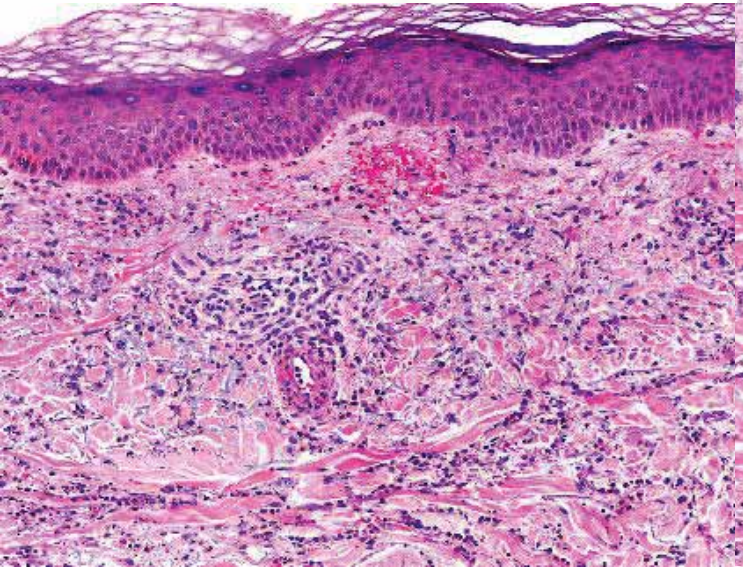
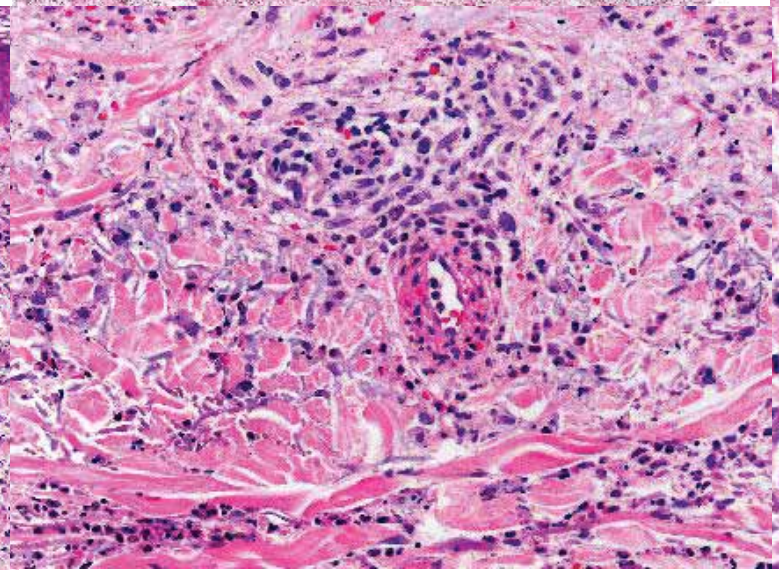
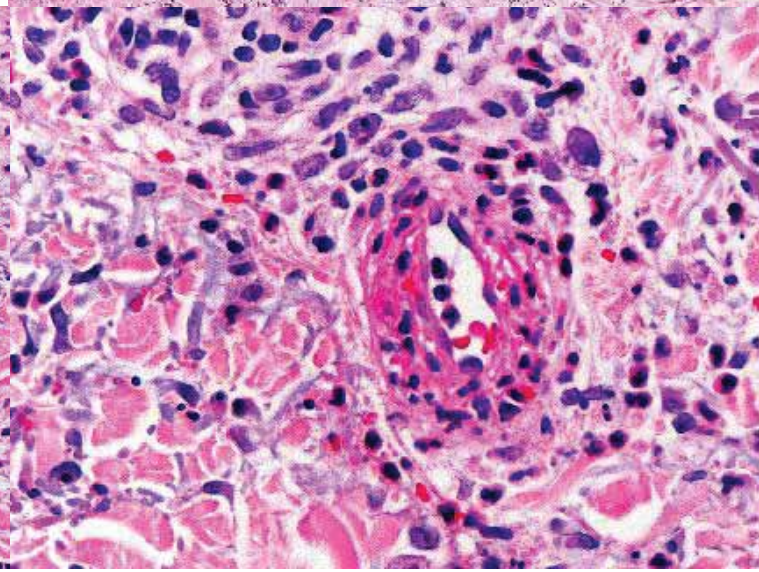
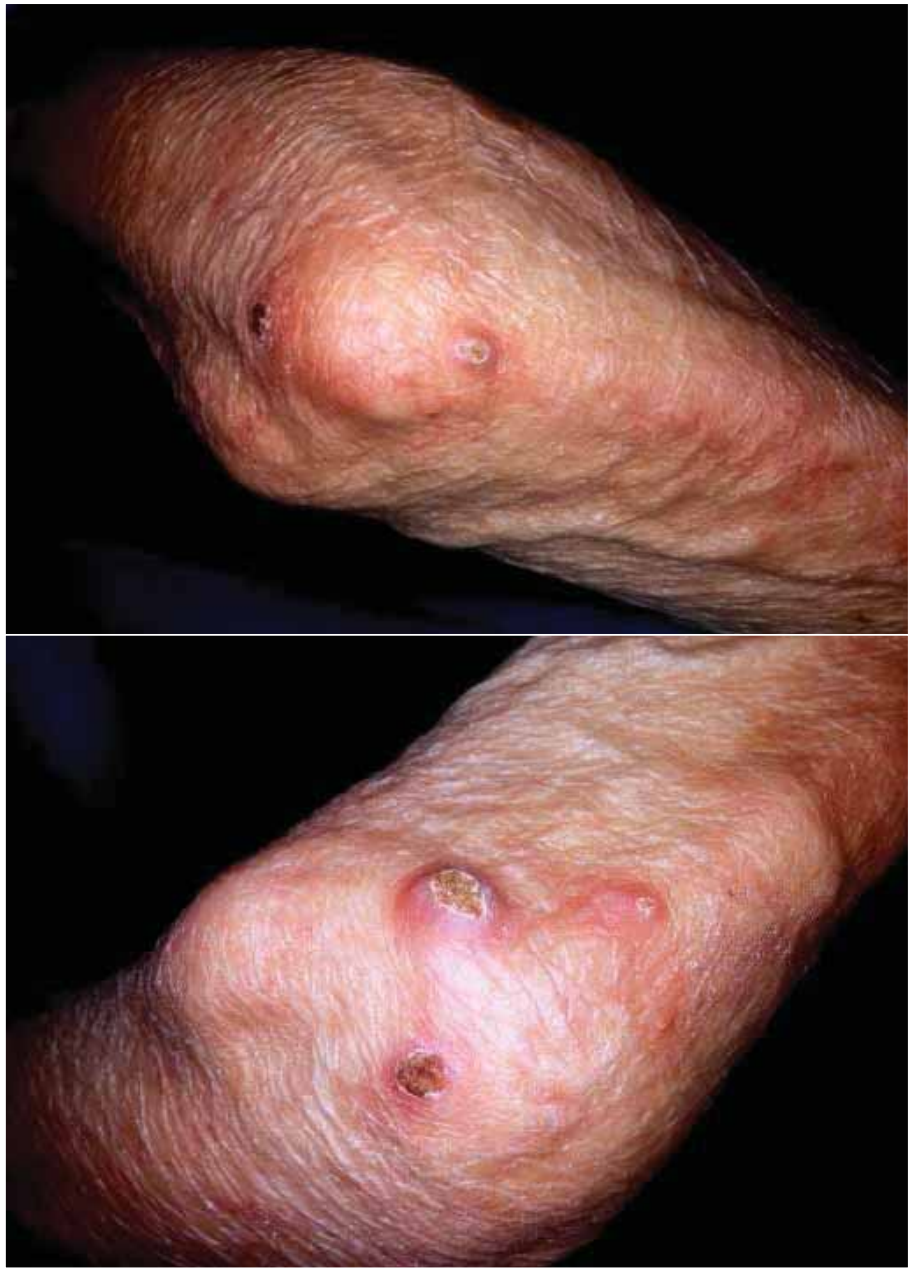
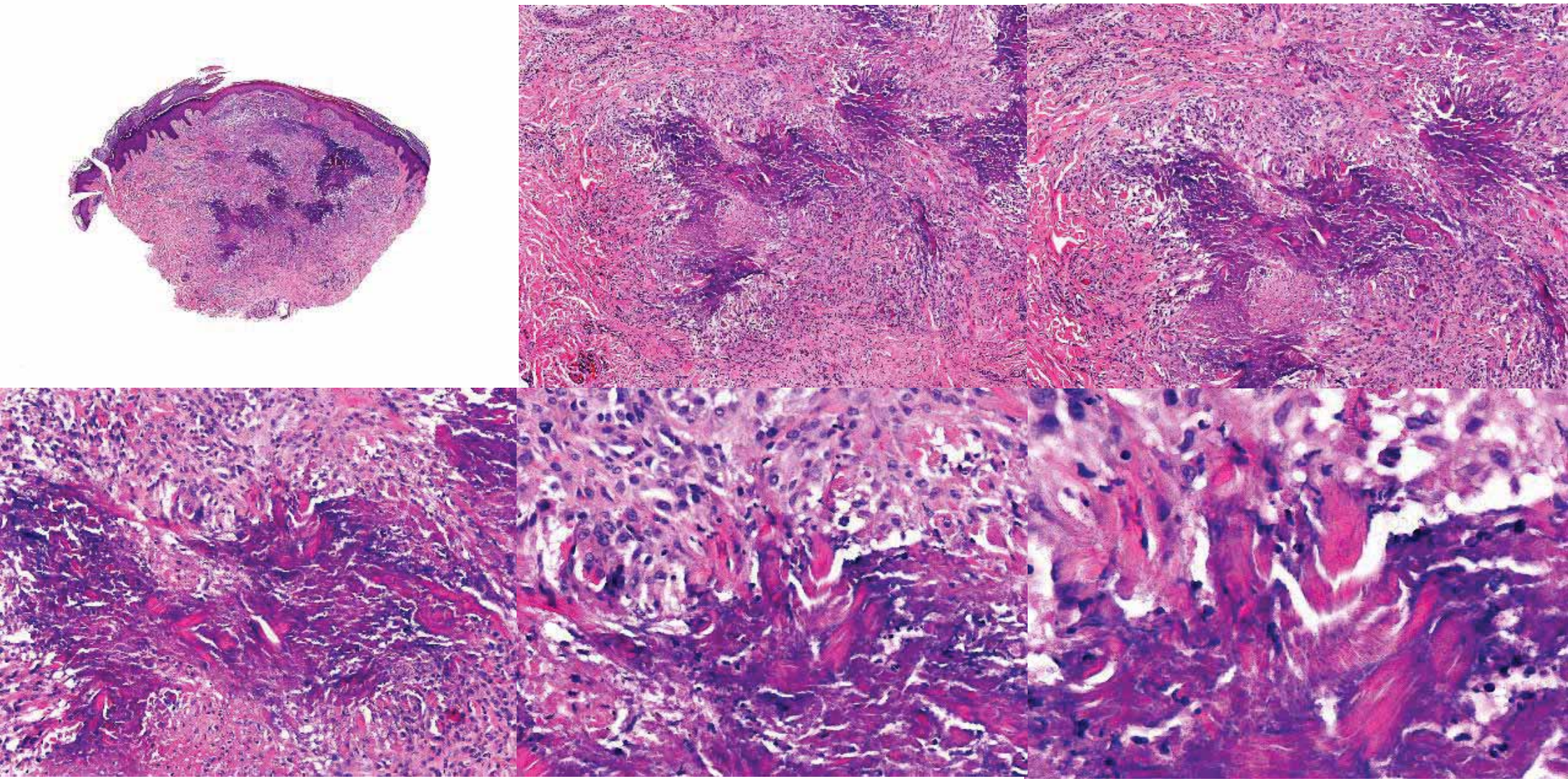
Background: Allergic granulomatosis of Churg-Strauss (Churg-Strauss syndrome) is a distinct clinical disease of multisystem vasculitis.
Objective: We characterize the clinical and histologic features of cutaneous findings in Churg-Strauss syndrome.
Methods: All patients with Churg-Strauss syndrome seen between 1976 and 1995 were retrospectively reviewed.
Results: Ninety patients with the diagnosis of Churg-Strauss syndrome were identified; 36 (40%) had cutaneous findings. Five patients (6%) had skin lesions as the initial manifestation. The most frequent cutaneous findings were purpura and petechiae on the lower extremities and cutaneous nodules and papules on the elbows. In 37 biopsy specimens from 29 patients, the most common findings were extravascular necrotizing granuloma (15 specimens) and leukocytoclastic vasculitis (16 specimens).
Conclusion: Cutaneous lesions in Churg-Strauss syndrome are common. Their characteristic clinical and histologic pattern may help establish the diagnosis.
(J Am Acad Dermatol 1997;37:199-203.)





OBSERVATION

Recurrent Cutaneous Necrotizing Eosinophilic Vasculitis

A Novel Eosinophil-Mediated Syndrome

Ko-Ran Chen, MD; Mark R. Pittelkow, MD; W. P. Daniel Su, MD; Gerald J. Gleich, MD; Walter Newman, PhD; Kristin M. Leiferman, MD

Background and Design: Review of skin biopsy specimens showing necrotizing vasculitis revealed three patients with small dermal vessel eosinophilic vasculitis and common clinical features characterized by glucocorticoid responsive pruritic erythematous, purpuric papules and angioedema associated with peripheral blood eosinophilia. Indirect immunofluorescent localization of eosinophil granule proteins, neutrophil granule proteins, and mast cell tryptase, electron-microscopic evaluation and immunoperoxidase staining for vascular cell adhesion molecule type 1, intercellular adhesion molecule type 1, endothelial-leukocyte adhesion molecule type 1, and very-late activation antigen type 4 were performed. Eosinophil-active cytokines in serum were evaluated by an eosinophil survival assay.

Observations: Eight skin biopsy specimens from the three patients all showed small-vessel necrotizing vasculitis with exclusive eosinophil infiltration. Ultrastructural study demonstrated degenerating eosinophils and eosinophil granules in proximity to damaged endothelium. The affected small vessels showed marked deposition of the toxic eosinophil granule major basic protein in the vessel walls and expression of vascular cell adhesion molecule type 1 and intercellular adhesion molecule type 1 on the endothelium with adherence of very-late activation antigen type 4–positive eosinophils. E-selectin staining was negative. The presence of interleukin 5 in serum available from one patient was detected by an eosinophil survival assay.

Conclusions: We studied three patients whose cutaneous lesions showed small-vessel eosinophilic vasculitis and who presented with recurrent glucocorticoid-responsive pruritic purpuric papules and angioedema. The presence of eosinophil-active cytokines in serum and the expression of vascular cell adhesion molecule type 1 on the endothelium of affected vessels may contribute to the selective adherence and localization of activated eosinophils. Subsequent release of cytotoxic proteins such as major basic protein may result in destruction of the endothelium in this unique syndrome.

(Arch Dermatol. 1994;130:1159-1166)

From the Department of Dermatology (Drs Chen, Pittelkow, Su, and Leiferman) and Division of Allergic Diseases and Internal Medicine and Department of Immunology (Dr Gleich), Mayo Clinic and Mayo Foundation, Rochester, Minn, and Otsuka Inc, Rockville, Md (Dr Newman). Drs Chen and Newman are now with the Kawasaki City (Japan) Hospital and Leukosite, Boston, Mass, respectively.

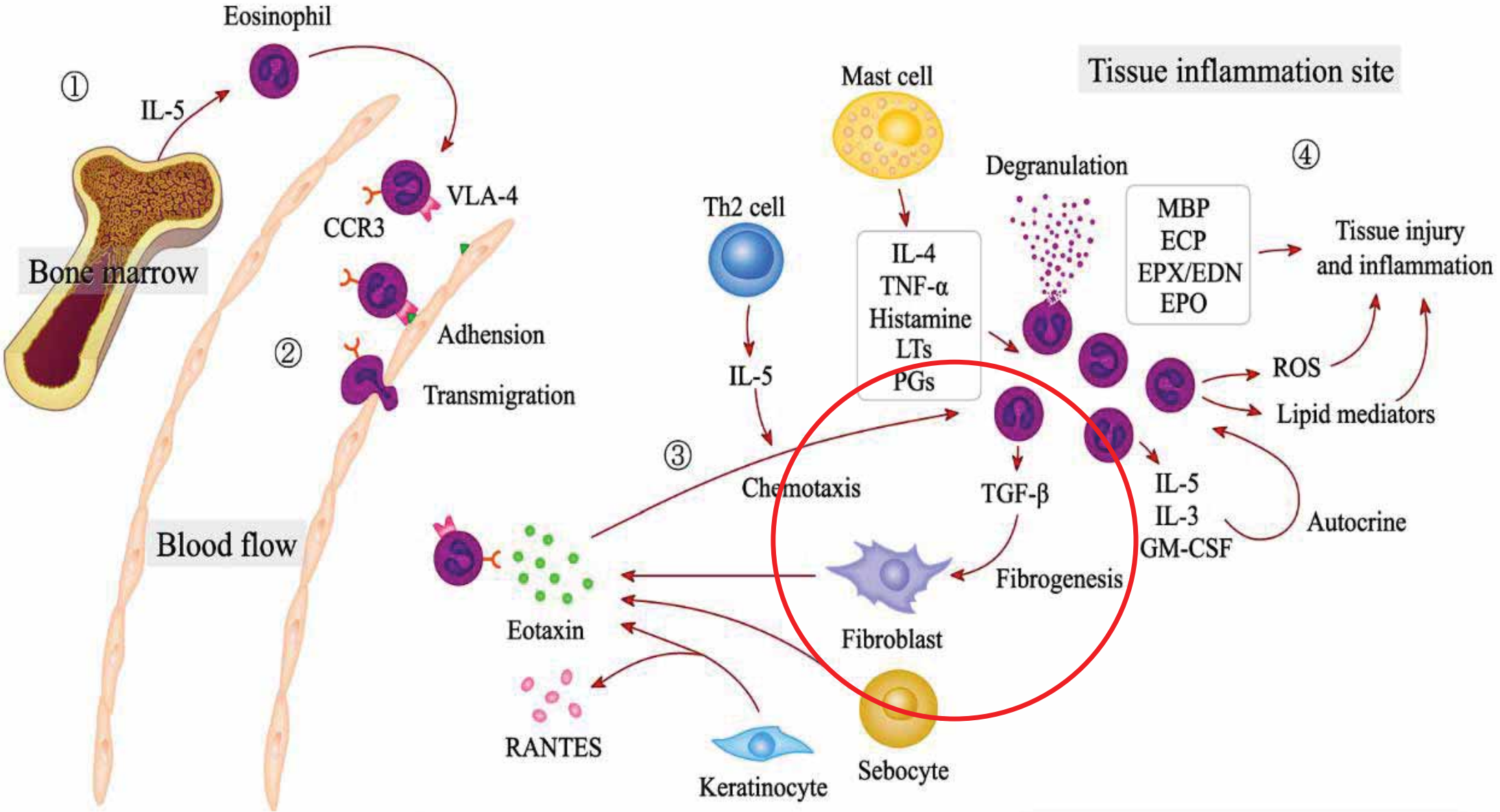
SINCE ZEEK'S classification in 1952, vasculitis has been defined on the basis of size and type of affected vessels as well as the predominant infiltrating cells. Although eosinophilic vasculitis of small- to medium-sized vessels is found in Churg-Strauss syndrome[1-3] and its variants,[4,5] necrotizing vasculitis of dermal small vessels with almost exclusive eosinophilic infiltration has not been described.[6,7]

We present three patients with idiopathic small-vessel eosinophilic vasculitis. This disease showed distinctive clinical manifestations, characteristic histopathologic findings, a dramatic response to systemic glucocorticoid treatment, and a benign chronic course. We believe that this is a distinct entity and should be distinguished from other types of vasculitis[4-7] and from the idiopathic hypereosinophilic syndrome.[8] Prolongation of eosinophil survival was observed with two patients' serum samples; ultrastructural and immunohistochemical studies showed eosinophil degranulation in and around the affected vessels.

See Methods on next page

EOSINOPHILIC DERMATOSES

Eosinophil location	Clinical pattern	Disorder
Epidermis	Eczematous	Atopic dermatitis Contact dermatitis Cutaneous T cell lymphoma Hypereosinophilic syndrome with cutaneous manifestations Langerhans cell histiocytosis Scabies and larva migrans
Dermo-epidermal junction	Macular and papular	Drug eruption DRESS
Papillary dermis	Urticarial	Urticaria Eosinophilic cellulitis (Wells syndrome) Episodic angioedema with eosinophilia (Gleich syndrome) Polymorphic eruption of pregnancy
Subepidermal/papillary dermis and hair follicles	Blisters and pustules	Bullous pemphigoid Pemphigus Incontinentia pigmenti Eosinophilic pustular folliculitis Erythema toxicum neonatorum
Papillary and reticular dermis	Papular and nodular	Insect bite Prurigo nodularis Eosinophilic annular erythema Eosinophilic cellulitis (Wells syndrome) Angiolymphoid hyperplasia with eosinophilia and Kimura disease Eosinophilic dermatosis associated with hematologic malignancy Primary cutaneous CD30+ lymphoproliferative disorders
Subcutis	Panniculitic	Erythema nodosum Parasitic panniculitis
Superficial vascular dermal plexus	Vasculitic	Eosinophilic vasculitis Granuloma faciale Eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease)
Fascia	Fibrosis and sclerosis	Localized scleroderma Systemic sclerosis Eosinophilic fasciitis


Eosinophil
①
IL-5
Bone marrow
VLA-4
CCR3
②
Adhension
Transmigration
Blood flow
Mast cell
Tissue inflammation site
Degranulation
④
Th2 cell
IL-4
TNF-α
Histamine
LTs
PGs
MBP
ECP
EPX/EDN
EPO
Tissue injury
and inflammation
IL-5
③
Chemotaxis
TGF-β
ROS
Lipid mediators
IL-5
IL-3
GM-CSF
Autocrine
Fibrogenesis
Eotaxin
Fibroblast
RANTES
Keratinocyte
Sebocyte

EOSINOPHILIC FASCIITIS

(Shulman disease)

- Clinical features:
  - Scleroderma-like induration of the skin, often after intense physical exertion.
  - Peripheral eosinophilia.
  - Hypergammaglobulinemia.
- Cutaneous lesions:
  - Abrupt onset of painful erythematous swelling and stiffness of the upper or lower extremities, with “peau d’orange” appearance in the skin surface.
  - “Groove” sign: a depression along the course of a vein or between muscle groups.
  - Severe skin induration and fascia fibrosis resulting in join contractures.
  - Some patients have associated hematologic disorders, solid tumors or autoimmune diseases.
- Histopathology: inflammatory and fibrous thickening of the fascia. Inflammatory infiltrate mostly composed of lymphocytes and plasma cells. Uncommonly, eosnophils are predominant in the infiltrate.