

Dermatitis herpetiformis

An autoimmune gluten-sensitive vesiculobullous dermatosis

Gluten-associated
autoimmunity

Papillary neutrophils

Granular IgA

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Learning outcomes

Mechanistic explanation

Morphologic interpretation

Immunofluorescence diagnosis

Differential reasoning

The diagnostic signature

Clinical pattern

Pruritic grouped extensor
eruption

H&E anatomy

Neutrophils at papillary tips

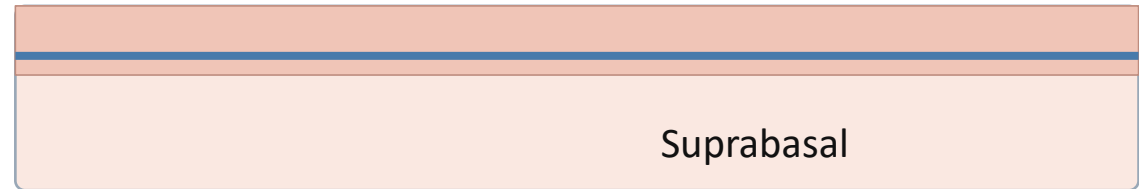
Direct IF

Granular papillary IgA



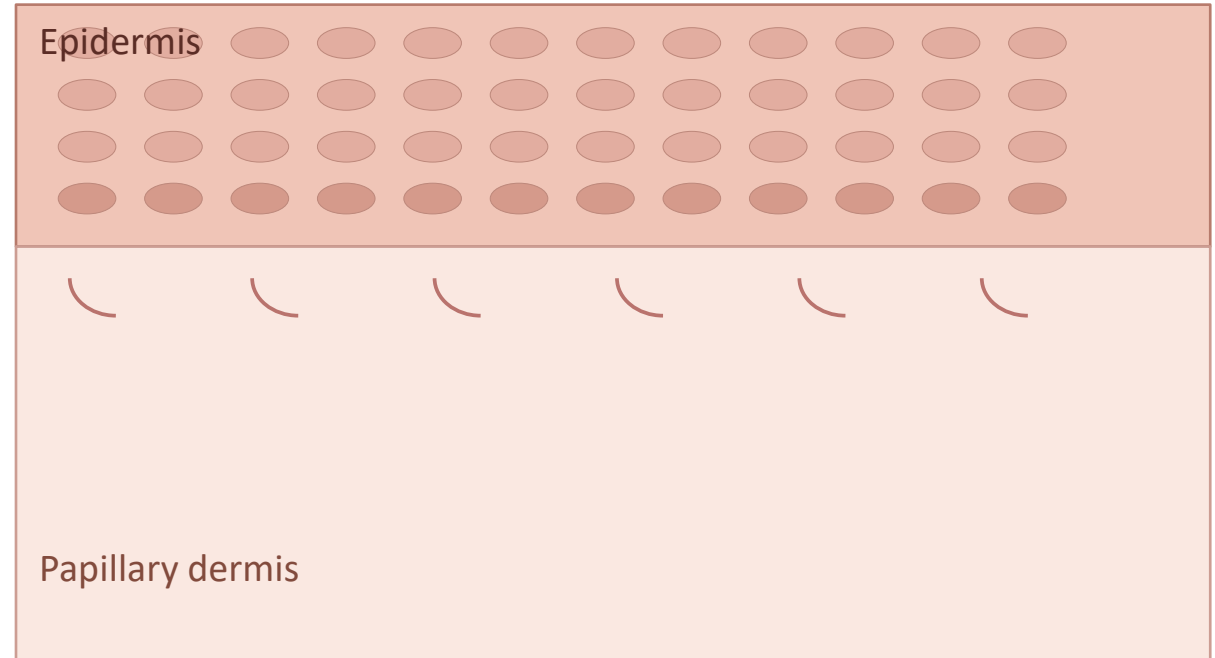
DH belongs among inflammatory blistering disorders

- Autoimmune injury occurs at the dermoepidermal interface.
- The separation plane is subepidermal:
The epidermis forms the blister roof.
- This is distinct from intraepidermal acantholysis in pemphigus.



Skin architecture: The relevant compartments

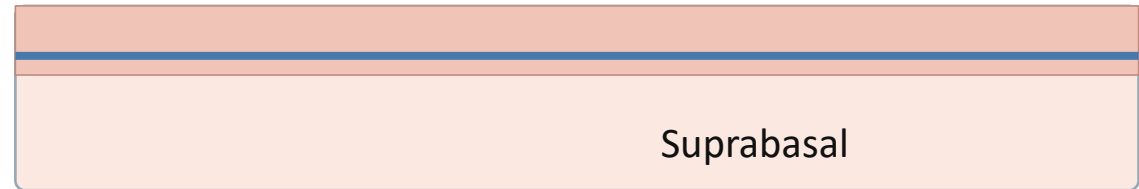
- Epidermis rests on a specialized basement-membrane zone.
- Dermal papillae project toward the basal epidermis.
- Anchoring structures stabilize the epidermis–dermis attachment.



Schematic — not a tissue specimen

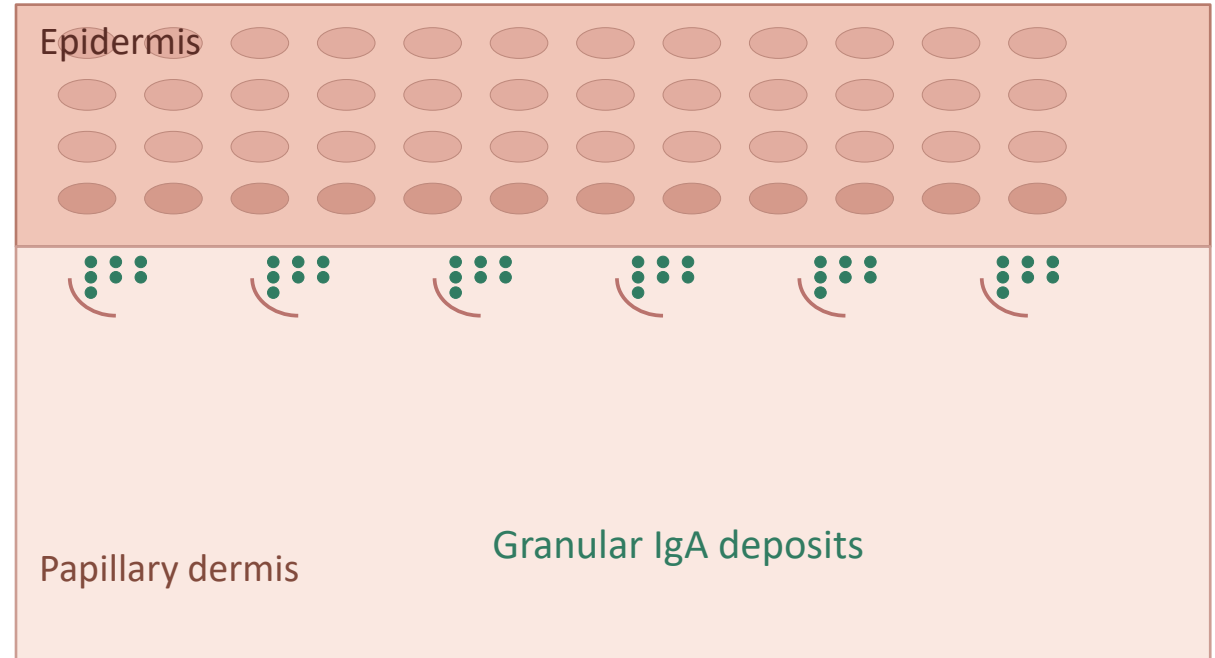
Why the blister roof remains intact

- Subepidermal cleavage lifts the full thickness of epidermis.
- The blister is initially mechanically more stable than a superficial split.
- Rupture and excoriation may later obscure the intact vesicle.



IgA autoimmunity is the defining mechanism

- IgA is the predominant immunoglobulin in the diagnostic deposits.
- Immune-mediated injury recruits inflammatory cells at the junction.
- Histologic injury occurs beneath, not between, keratinocytes.



Schematic — not a tissue specimen

Who develops the disease?

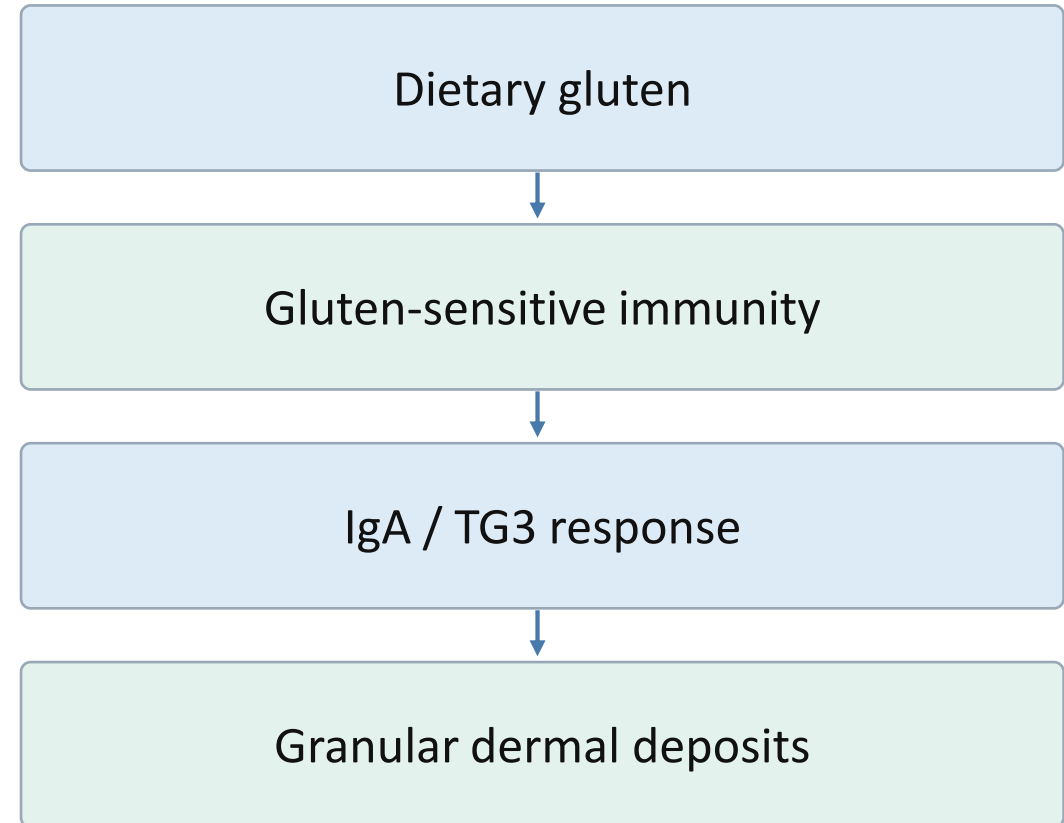
- Male predominance and frequent presentation in the third or fourth decade.
- Contemporary cohorts also include older adults; Age distribution varies by population.
- Demographics support suspicion but cannot establish or exclude DH.

INTERPRET IN CONTEXT

Clinical phenotype
+ immunopathology
+ supportive tests

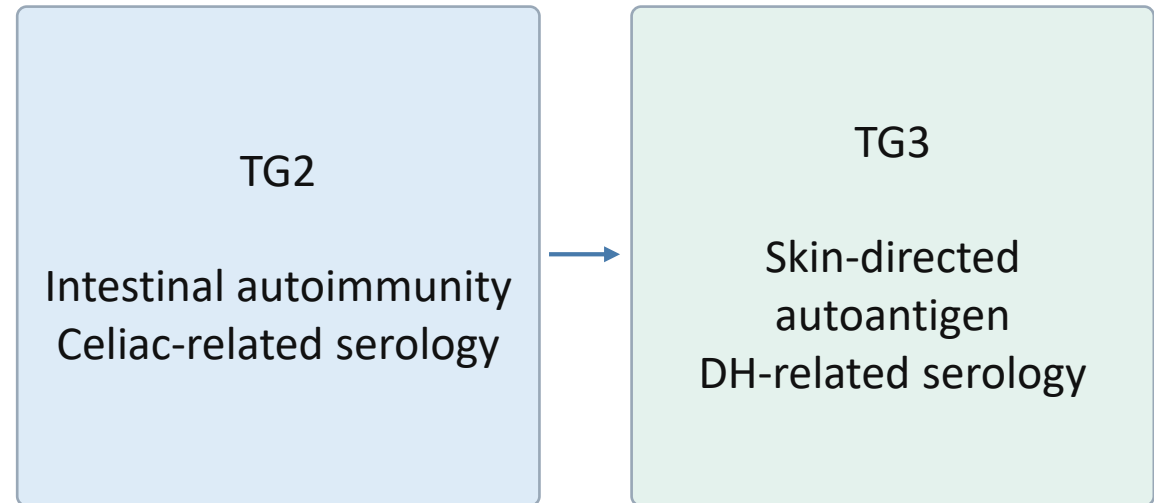
The celiac disease association

- A greater than 100-fold increased DH risk in people with celiac disease.
- DH is widely considered a cutaneous manifestation of gluten-sensitive enteropathy.
- Cutaneous symptoms may dominate even when bowel symptoms are minimal.



Classical and contemporary autoantigens

- IgA reactivity with reticulin / anchoring-fibril components.
- Contemporary literature identifies epidermal transglutaminase (TG3) as the principal DH autoantigen.
- Distinguish the textbook framing from the newer molecular explanation.



Related—not interchangeable—targets

Inherited susceptibility: HLA-DQ2 and HLA-DQ8

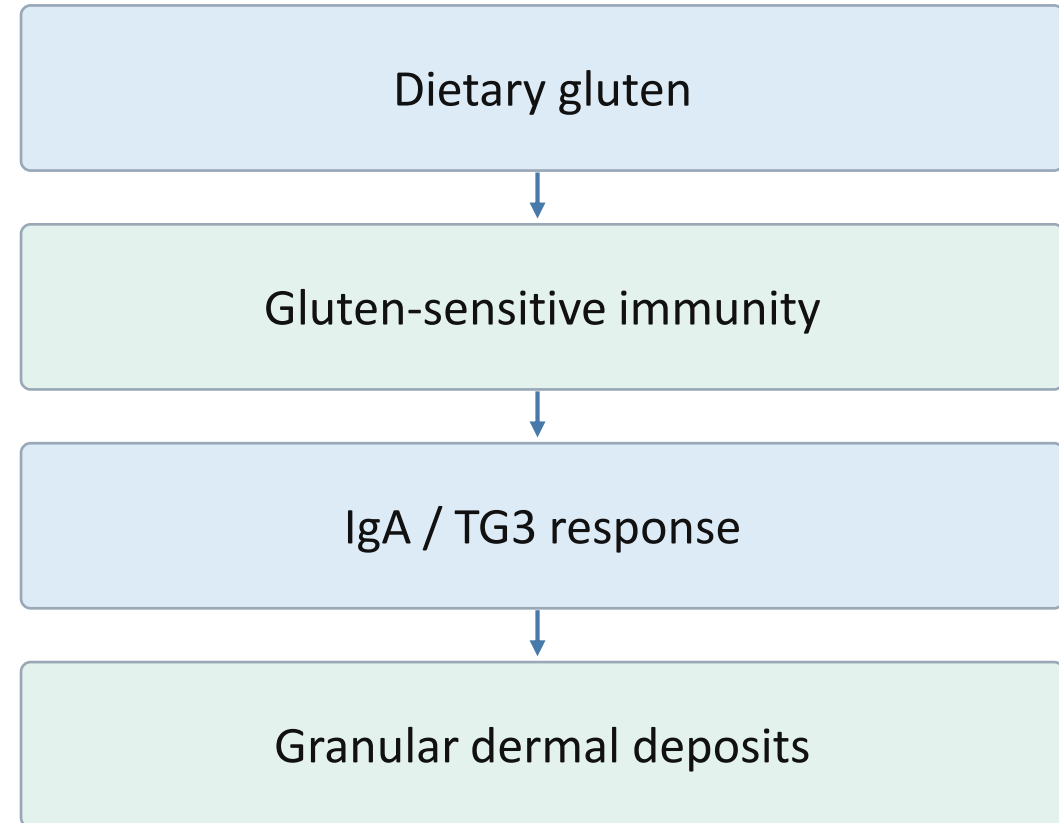
- These HLA haplotypes facilitate gluten-associated immune responses.
- Their presence is common in the general population and is not diagnostic.
- Absence can help exclude the disease in an equivocal evaluation.

INTERPRET IN CONTEXT

Clinical phenotype
+ immunopathology
+ supportive tests

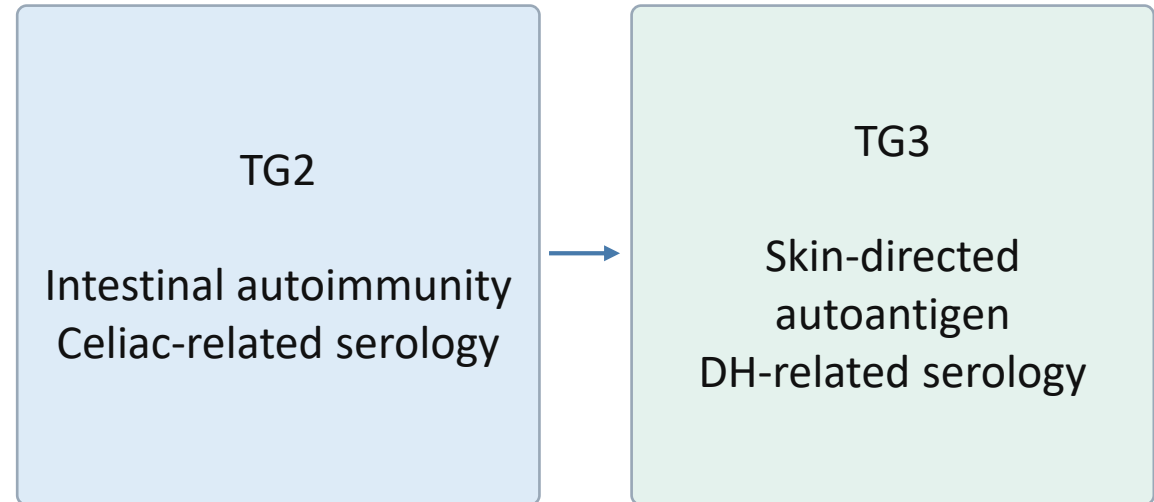
Dietary gluten initiates the gut–skin axis

- Gluten-related peptides provoke a mucosal immune response in predisposed hosts.
- Celiac-associated immune dysregulation precedes or accompanies DH.
- Cutaneous disease is linked to persistent gluten exposure.



Tissue transglutaminase versus epidermal transglutaminase

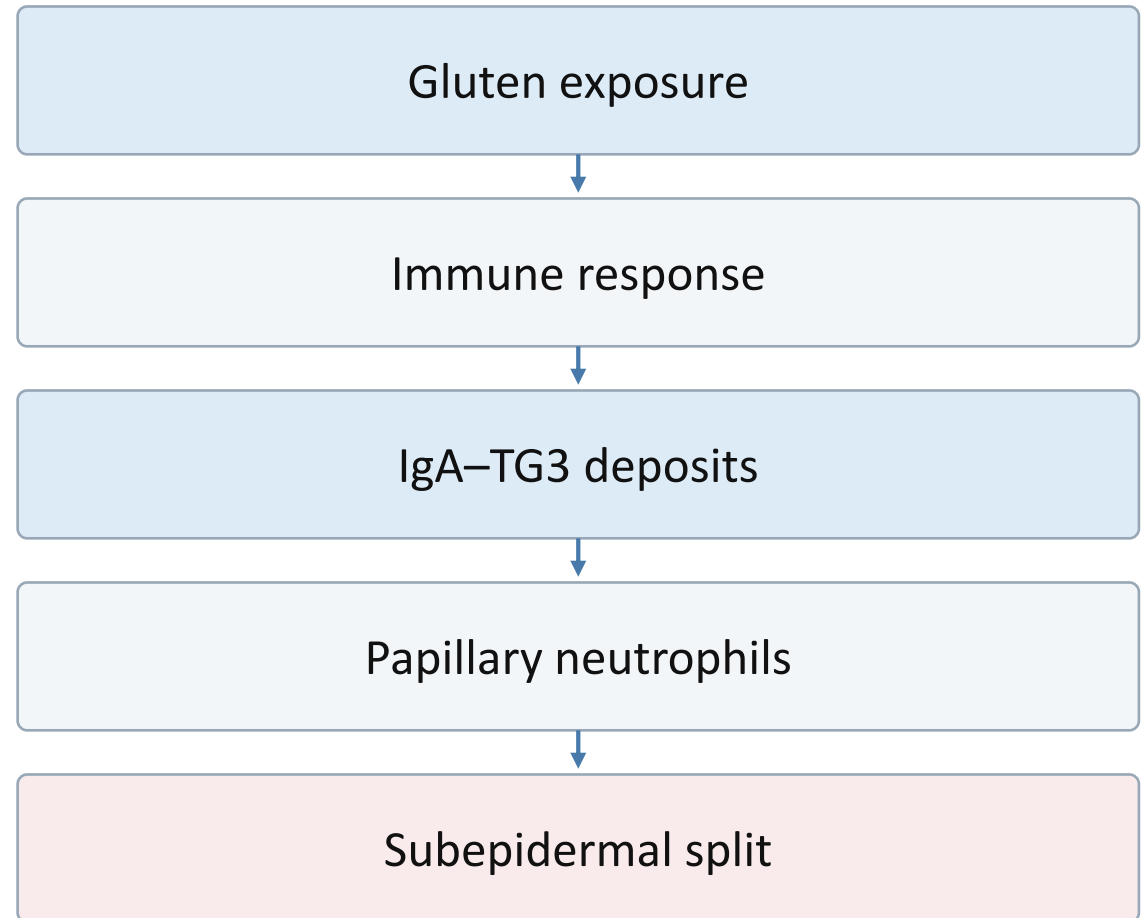
- TG2: Central autoantigen in celiac enteropathy and a common serologic target.
- TG3: Primary cutaneous autoantigen associated with DH.
- Serologic and tissue autoantigens overlap, but are not identical.



Related—not interchangeable—targets

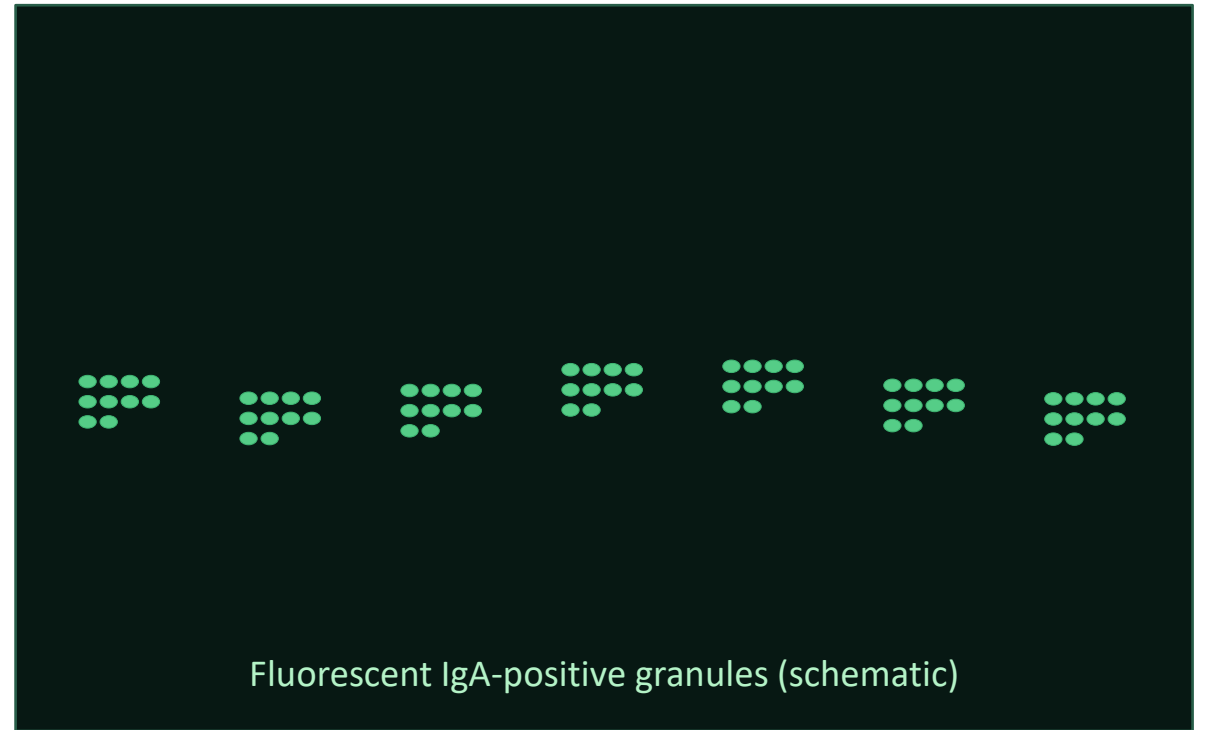
A mechanistic sequence from gluten to skin injury

- Gluten exposure in a susceptible host.
- Gluten-associated autoimmunity with IgA targeting TG3.
- Granular dermal IgA deposition and neutrophil-dominant injury.



Where IgA accumulates

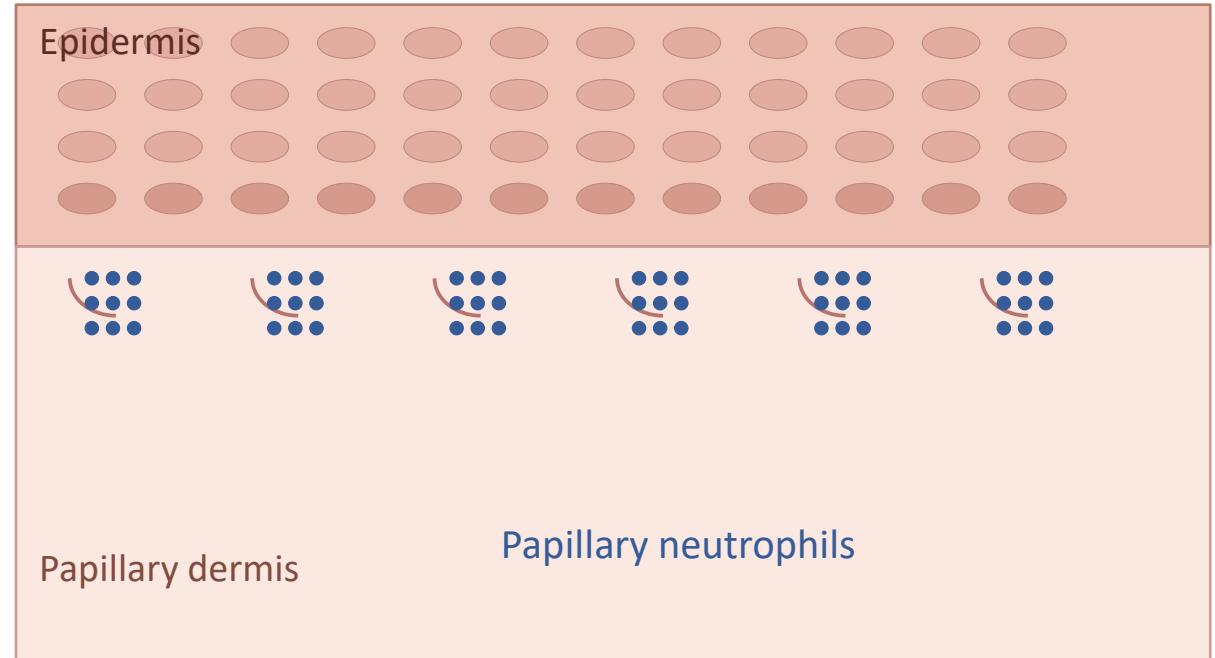
- The characteristic pattern is discontinuous and granular.
- Deposits emphasize the tips of the dermal papillae.
- Unlike pemphigoid, the defining pattern is not a smooth continuous IgG line.



Read the deposit pattern and its anatomic location

Why neutrophils are recruited

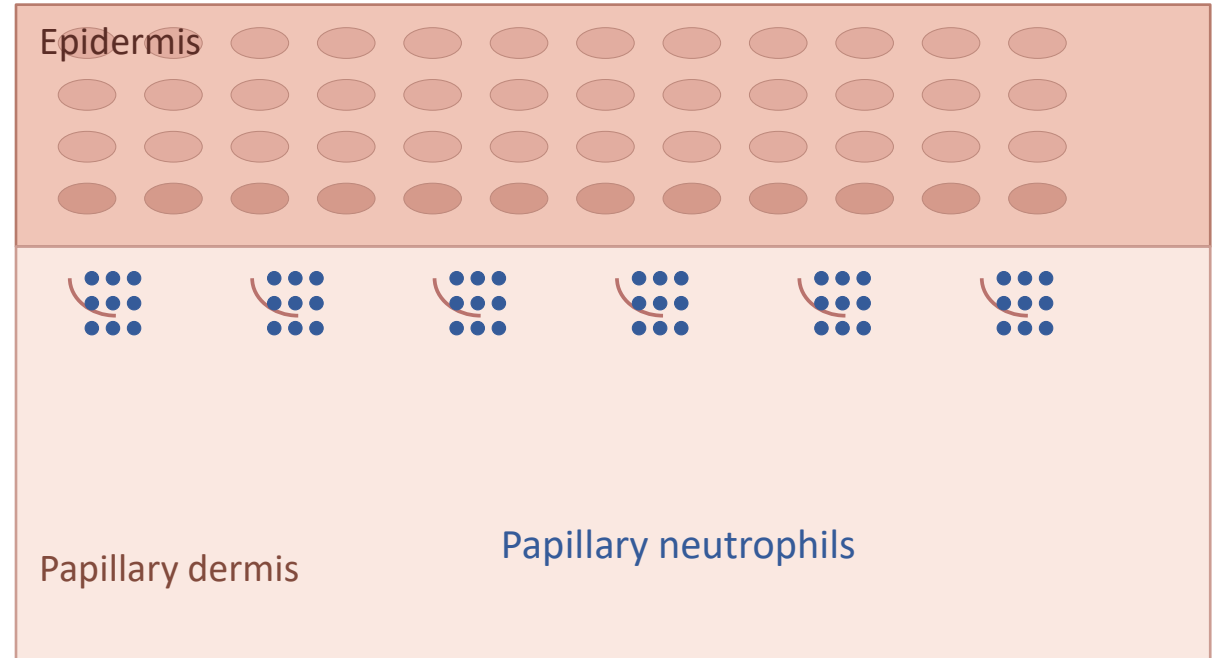
- Granular immune deposition is associated with a local inflammatory reaction.
- Neutrophils concentrate in the papillary dermis.
- Inflammatory injury damages the basal junction and facilitates cleavage.



Schematic — not a tissue specimen

Papillary microabscesses: The early microscopic clue

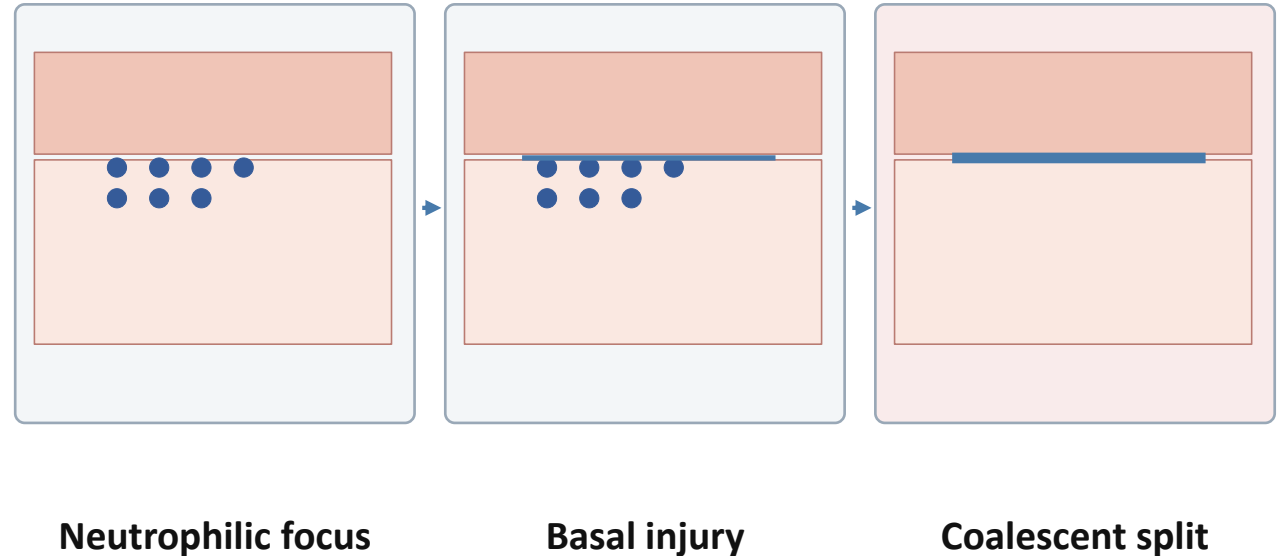
- Dense clusters of neutrophils form in papillary tips.
- Fibrin may accompany the neutrophils.
- The overlying epidermis may still be largely attached.



Schematic — not a tissue specimen

From microabscess to vesicle

- Early papillary inflammation causes basal vacuolization.
- Focal separations develop at the dermoepidermal junction.
- Adjacent foci can merge into an established subepidermal blister.



Pruritus is often the dominant complaint

- The lesions are intensely itchy, commonly before vesicles are noticed.
- Persistent scratching creates erosions and crusts.
- Clinical severity may be disproportionate to the number of intact blisters.

Grouped papules and vesicles



Intense itch → scratching



Erosions, crust and pigmentation

Grouped vesicles and urticarial plaques

- The eruption contains small, grouped vesicles on erythematous or urticarial skin.
- Papules, erosions, and excoriations can coexist.
- The term “herpetiformis” describes arrangement—not herpesvirus infection.

Grouped papules and vesicles



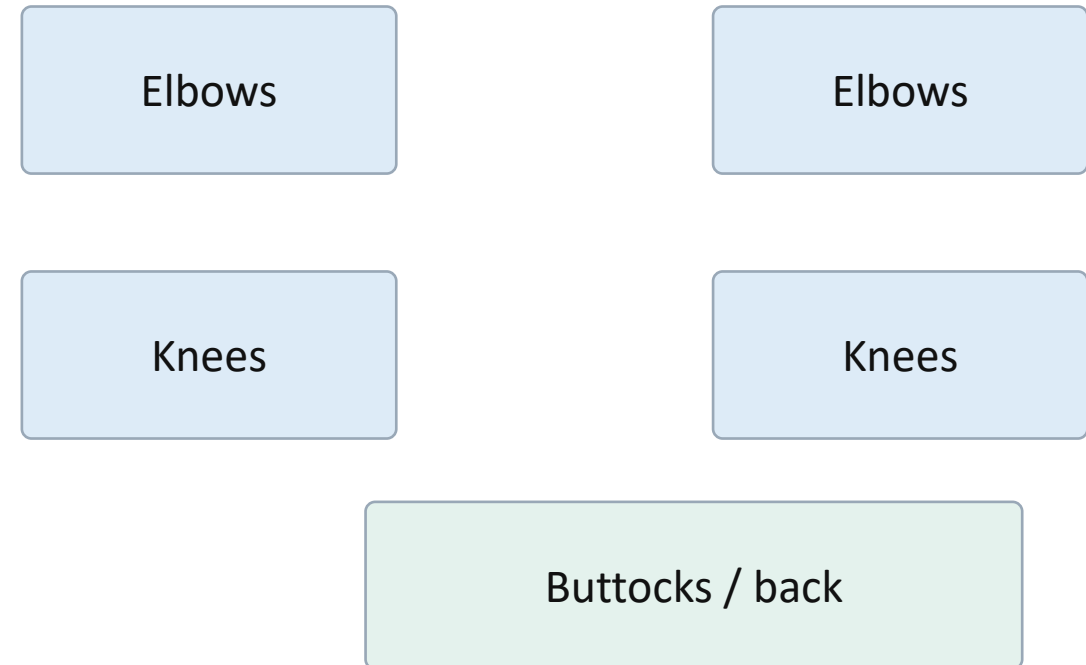
Intense itch → scratching



Erosions, crust and pigmentation

Typical distribution: Extensor predominance

- Elbows and knees are characteristic sites.
- Buttocks and upper back are also common.
- The bilateral, symmetric pattern adds diagnostic weight.



Mirror-image involvement is common

Symmetry as a clinical discriminator

- Lesions frequently occur on corresponding sites on both sides.
- Symmetry should prompt an autoimmune / systemic mechanism in context.
- Asymmetry or limited sites do not automatically exclude DH.

Elbows

Elbows

Knees

Knees

Buttocks / back

Mirror-image involvement is common

The scratch can erase the blister

- Intact vesicles may be absent in a heavily excoriated eruption.
- Crust, scratch marks and postinflammatory changes can dominate.
- Biopsy selection should avoid a denuded, heavily scratched center.

Grouped papules and vesicles



Intense itch → scratching



Erosions, crust and pigmentation

Appearance in darker skin tones

- The eruption may look hyperpigmented rather than vividly erythematous.
- Excoriations and residual pigment can be prominent.
- Evaluate site, symmetry, grouping and pruritus—not erythema alone.

Grouped papules and vesicles



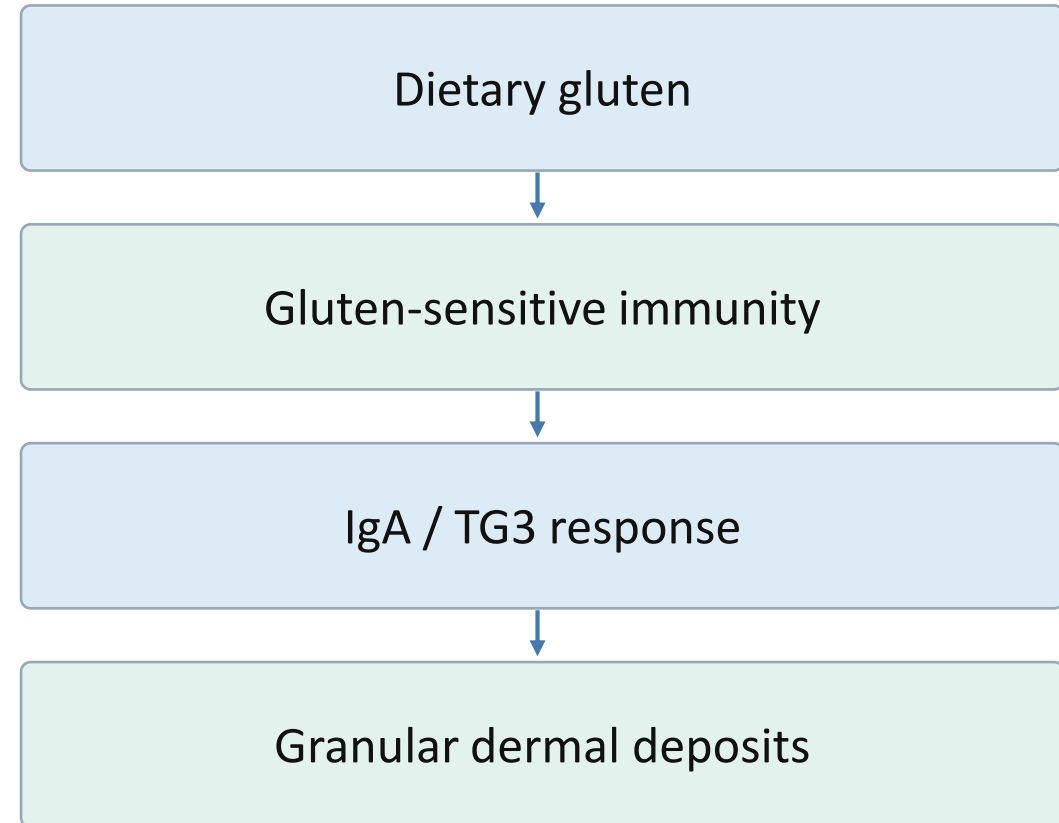
Intense itch → scratching



Erosions, crust and pigmentation

Few gastrointestinal symptoms do not exclude DH

- Many patients have intestinal pathology without overt diarrhea.
- A skin presentation may be the first recognized sign of gluten sensitivity.
- Gastrointestinal assessment follows confirmed disease even without bowel complaints.



Why the name is misleading

- “Herpetiform” refers to grouped vesicles resembling herpes distribution.
- DH is not caused by herpes simplex or varicella-zoster virus.
- Pruritus, extensor symmetry, and granular IgA favor DH over herpes infection.

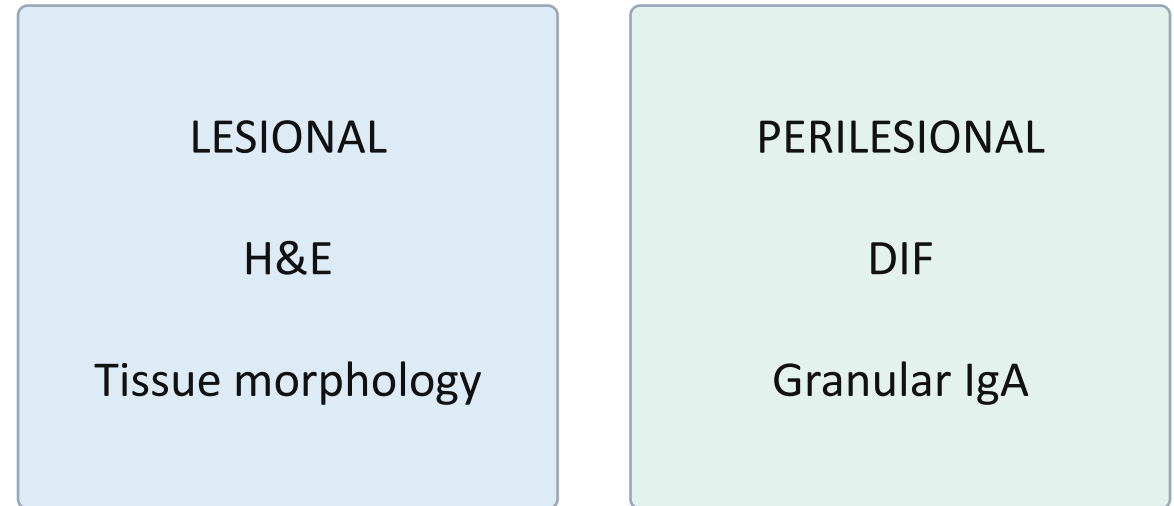
Pruritus is nonspecific

Symmetric extensor papulovesicles suggest DH

Definitive classification needs immunopathology

Two samples answer two different questions

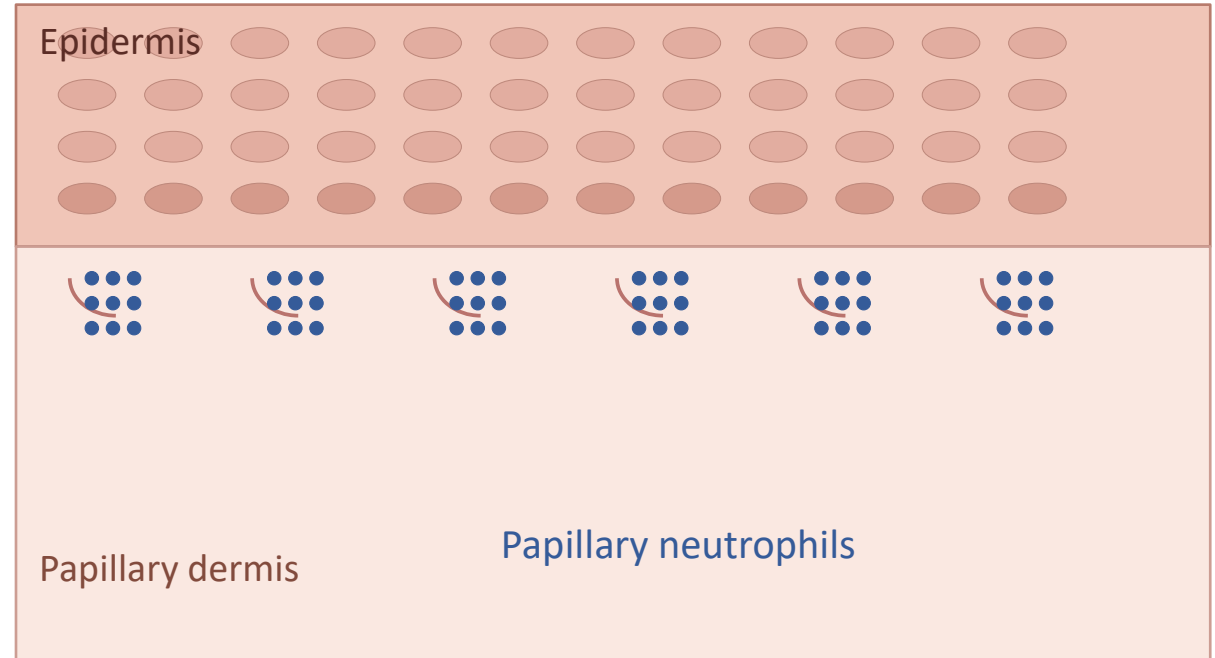
- Lesional skin in formalin:
Hematoxylin–eosin morphology.
- Perilesional normal-appearing skin in
DIF medium: Tissue-bound IgA.
- A poorly selected specimen can yield a
misleading negative study.



Separate biopsies • correct medium and site

Read the lesional H&E in a fixed sequence

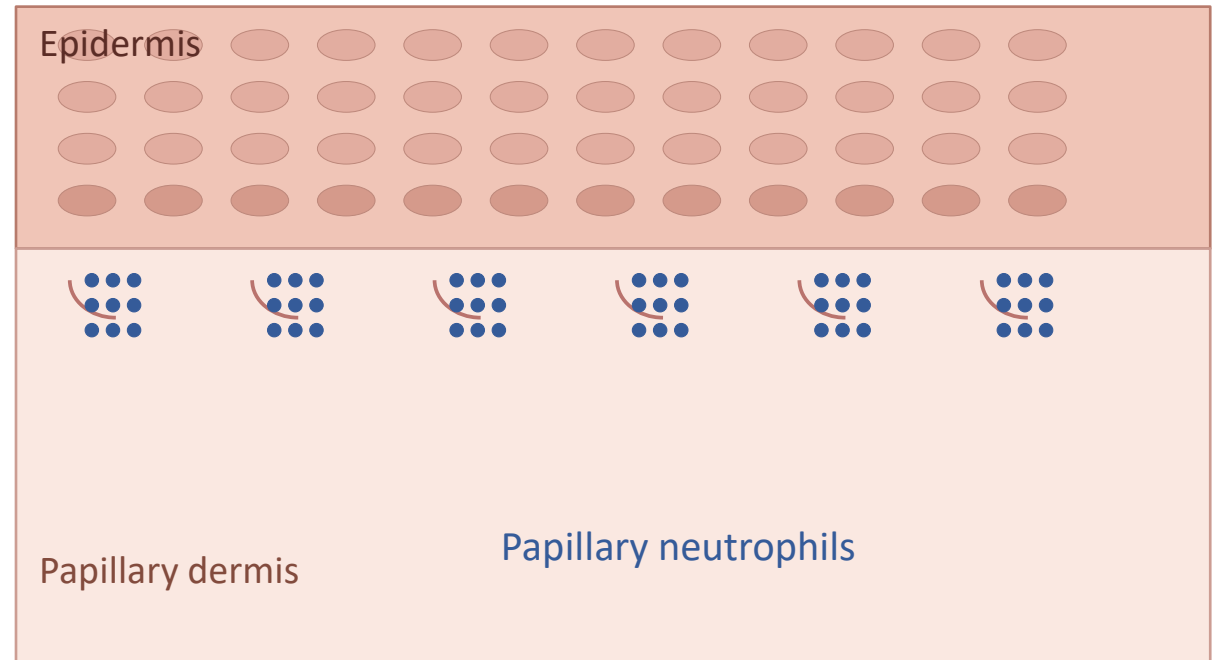
- First: Identify intraepidermal versus subepidermal separation.
- Second: Inspect neutrophils within individual papillary tips.
- Third: Assess vacuolization, edema, fibrin and secondary scratching.



Schematic — not a tissue specimen

Early histology: Dermal papillary inflammation

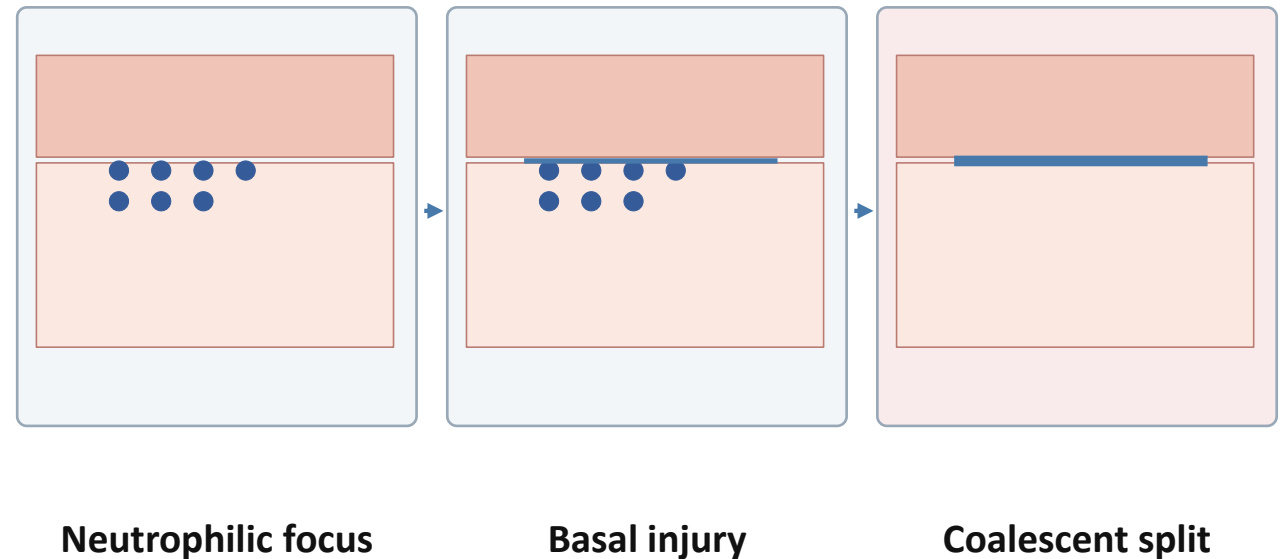
- Neutrophils collect at the apex of papillae.
- Small superficial foci precede a fully developed blister.
- Subtle changes require careful inspection of multiple levels.



Schematic — not a tissue specimen

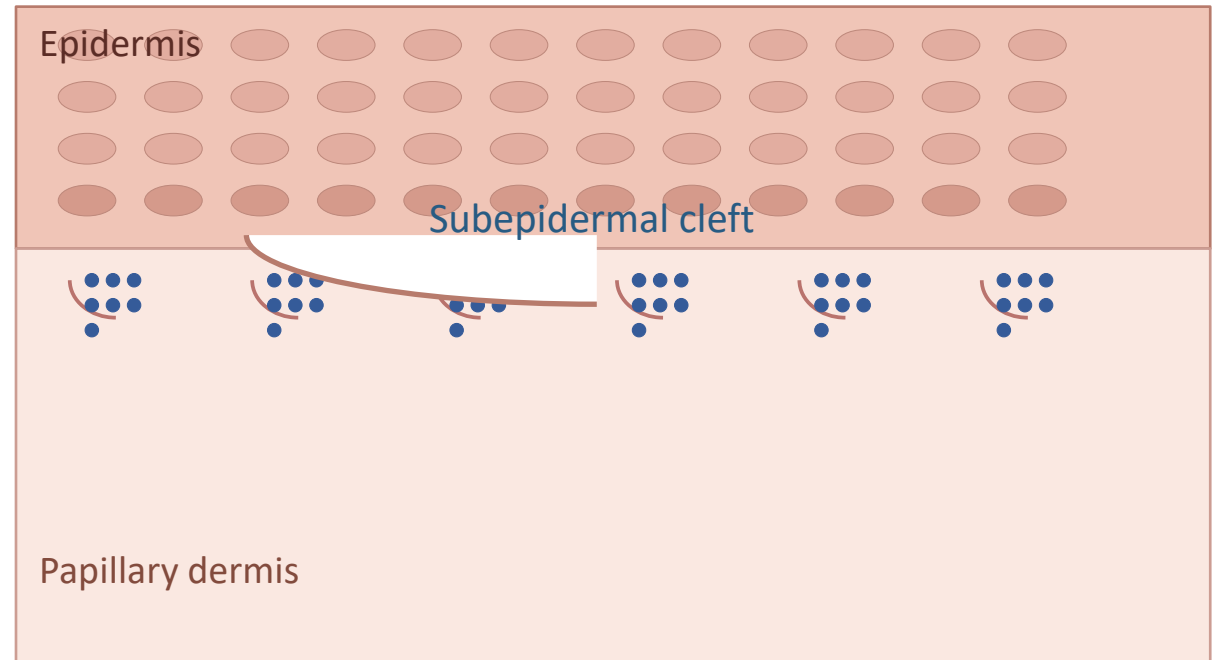
Evolving lesion: Basal injury and cleavage

- Vacuolization appears in the basal keratinocytes.
- Multiple focal junctional defects develop.
- The epidermis lifts as damage coalesces.



Established lesion: Subepidermal cavity

- The epidermis forms the complete roof of the blister.
- The cavity may contain inflammatory cells and proteinaceous fluid.
- Papillary neutrophilic collections support DH when identifiable.



Schematic — not a tissue specimen

Inflammatory-cell pattern has diagnostic value

- Neutrophils in dermal papillae are a hallmark.
- A minority of eosinophils may also be encountered in lesional biopsies.
- Neutrophilic histology alone does not uniquely identify DH.

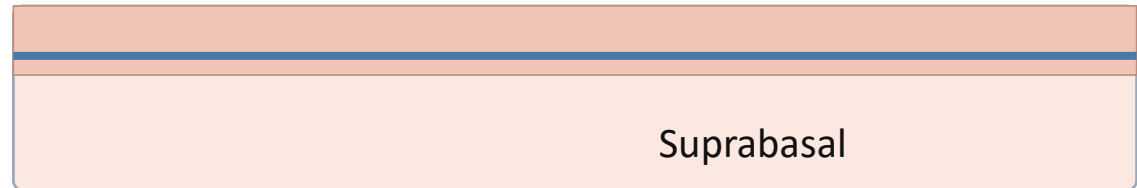
Neutrophils
Papillary
microabscesses

Eosinophils
May be present but are
not defining

Pattern + location outperform cell type alone

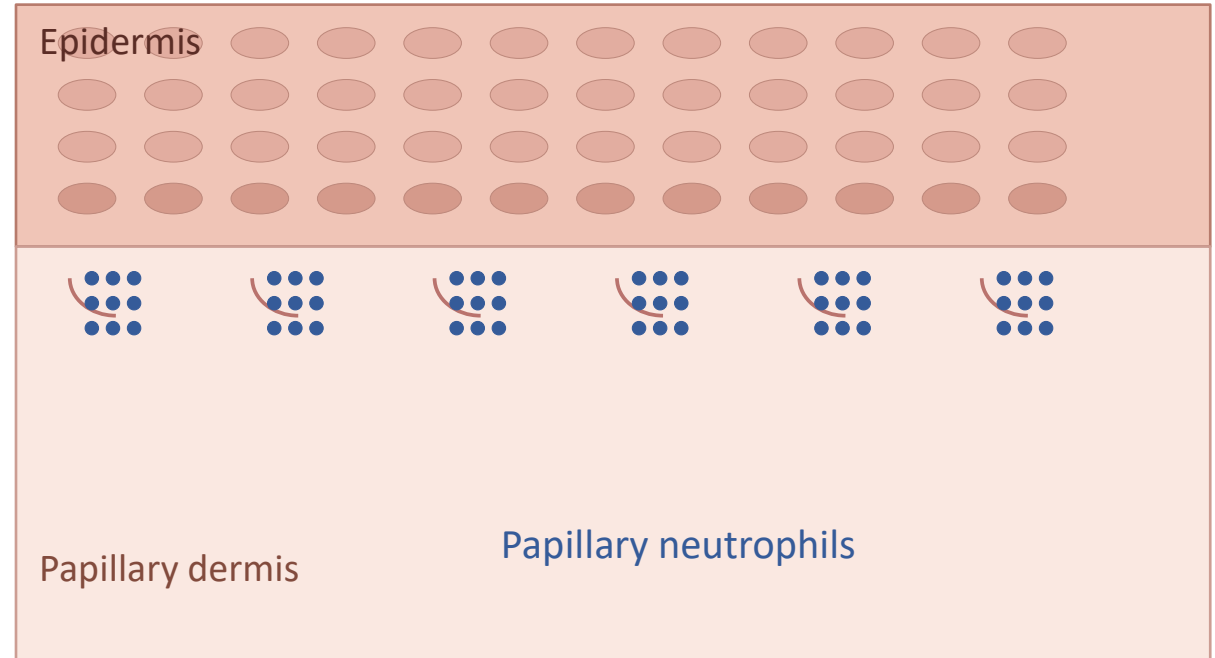
Acantholysis is not the principal DH lesion

- Acantholysis is loss of cohesion among epidermal keratinocytes.
- Pemphigus produces intraepidermal acantholytic blisters.
- DH produces interface injury with subepidermal separation.



Why H&E findings can be insufficient

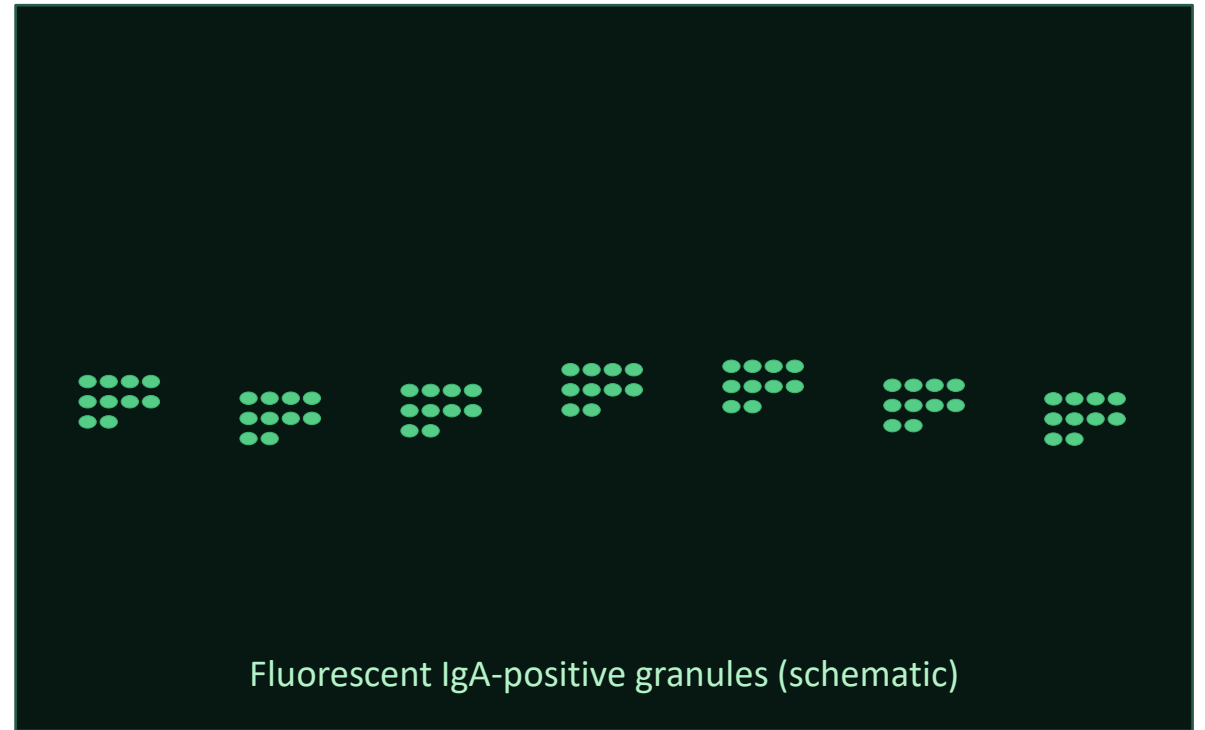
- Scratch injury can conceal the primary blister morphology.
- Early lesions may show papillary inflammation without a definitive cavity.
- Histology and clinical context should be integrated with DIF.



Schematic — not a tissue specimen

Direct immunofluorescence: What is examined?

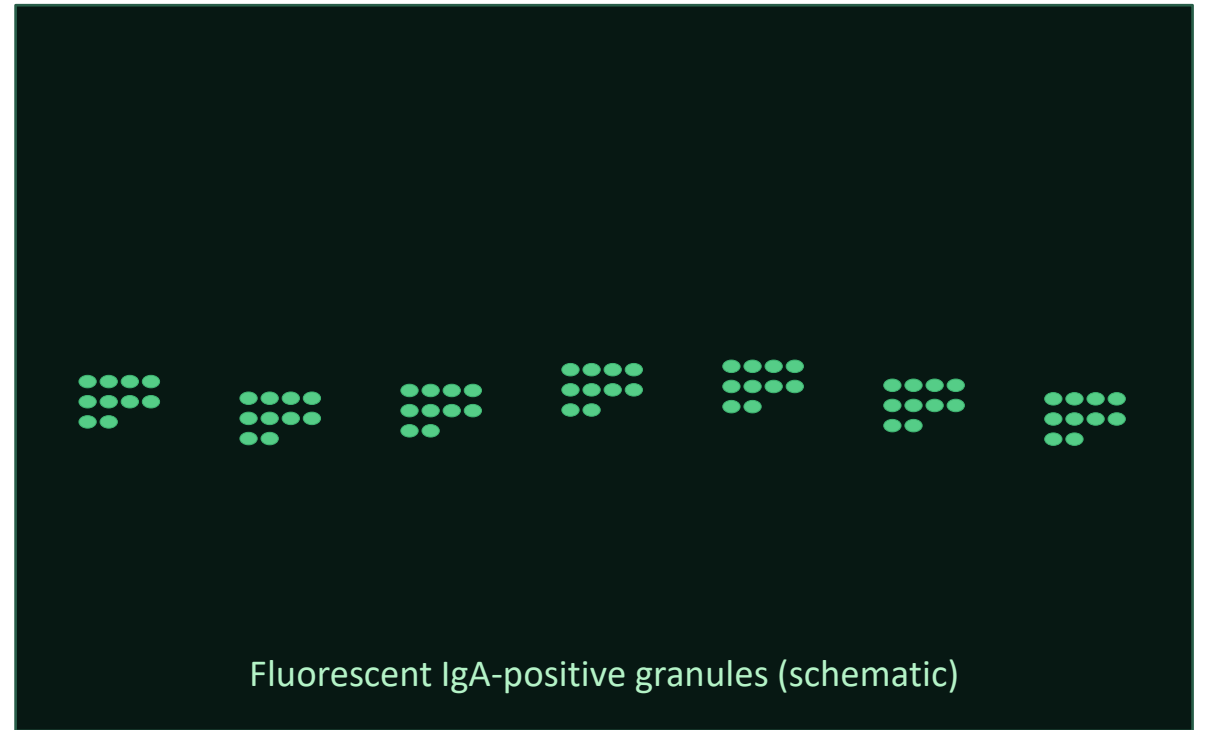
- DIF detects immunoreactants already deposited within patient skin.
- An anti-human IgA fluorescent reagent highlights their tissue location.
- Pattern and anatomic compartment are interpreted together.



Read the deposit pattern and its anatomic location

Granular papillary IgA is the central diagnostic finding

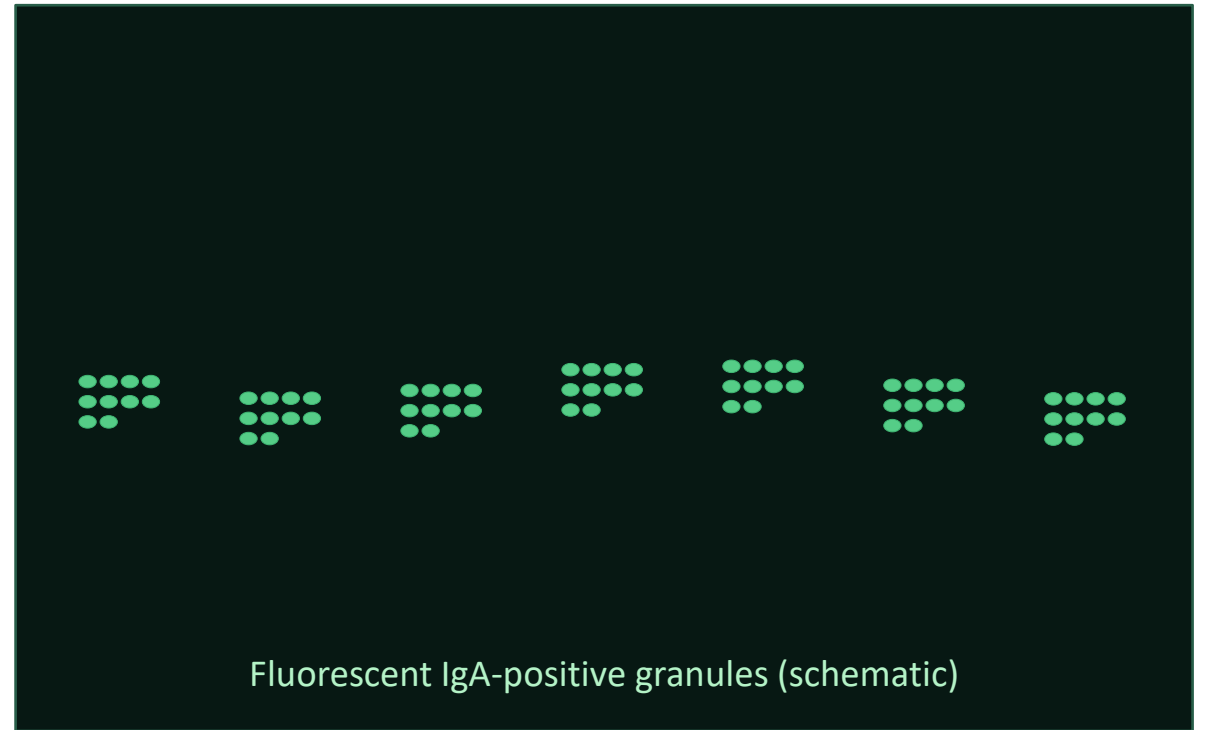
- Granular IgA appears in the papillary dermis, especially papillary tips.
- Deposits are discontinuous rather than a smooth linear band.
- A compatible DIF strongly supports the diagnosis of DH.



Read the deposit pattern and its anatomic location

Granular IgA may track the junction

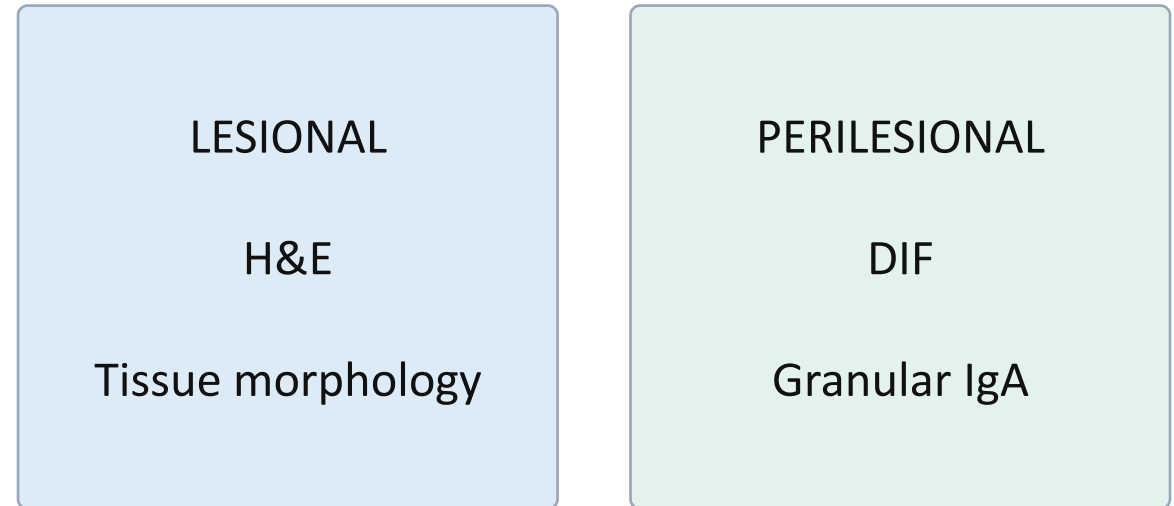
- Papillary-tip deposits are classic.
- Other described DH patterns include granular deposits along the junction.
- Do not equate every junctional IgA signal with a continuous linear IgA disease pattern.



Read the deposit pattern and its anatomic location

Biopsy site for DIF: Perilesional skin

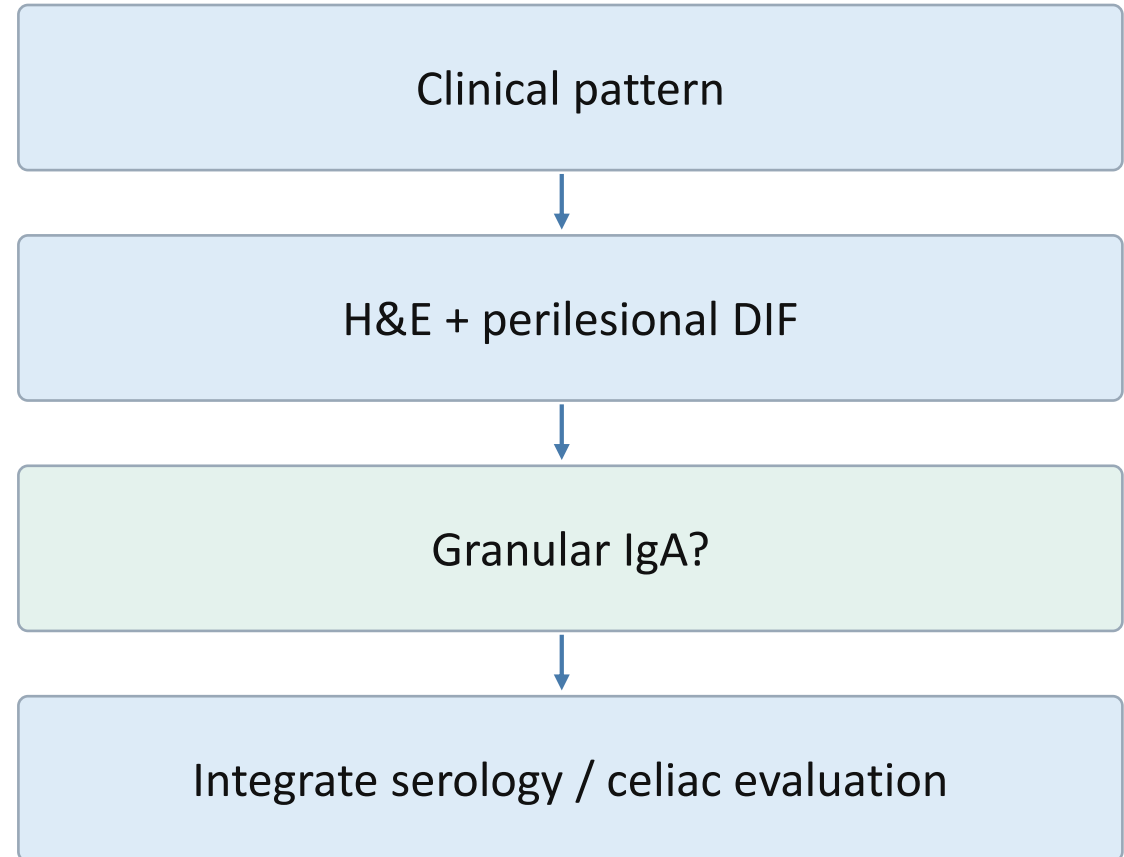
- Sample normal-appearing skin immediately adjacent to an active lesion.
- Avoid a ruptured blister or a severely inflamed/excoriated area.
- Use the laboratory's dedicated DIF transport protocol, not routine formalin.



Separate biopsies • correct medium and site

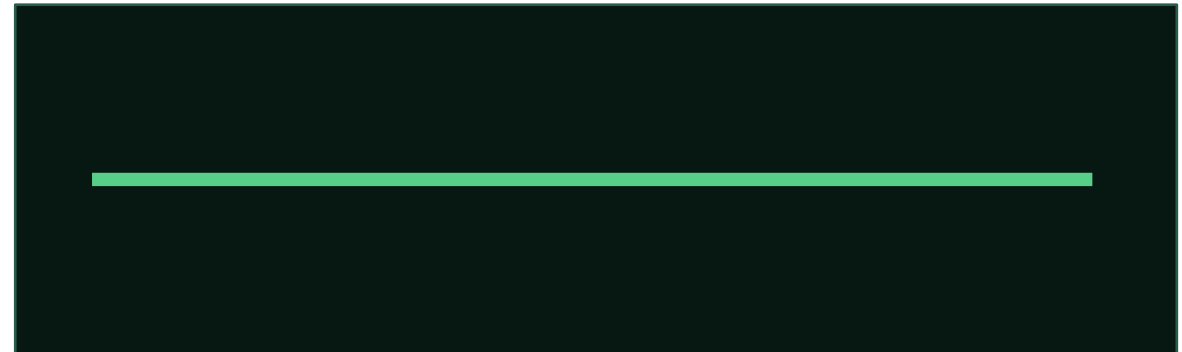
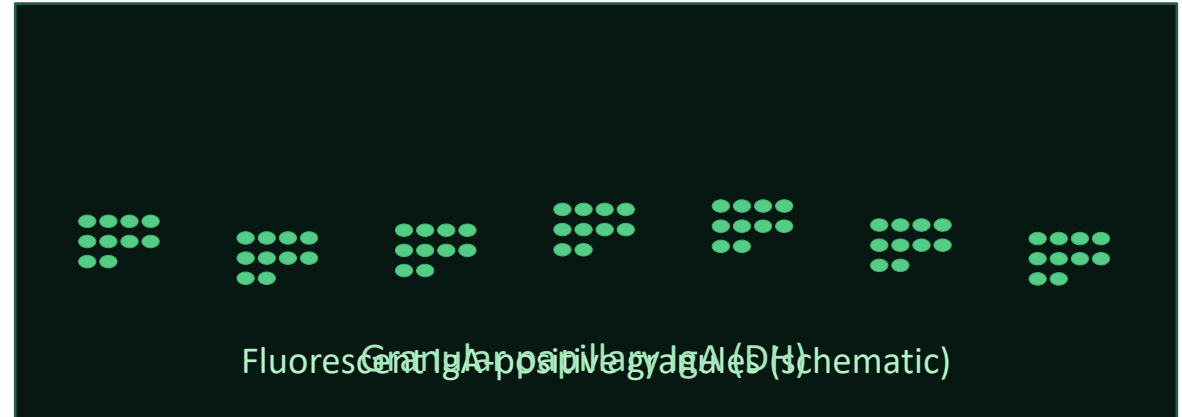
A negative DIF requires clinical interpretation

- Check whether sampling and handling were appropriate.
- Long-term gluten avoidance can reduce IgA deposits and test positivity.
- If suspicion remains high, consider expert review and repeat properly sited DIF.



Granular versus linear deposition

- DH: Granular IgA emphasized at papillary tips.
- Linear IgA bullous dermatosis: Linear IgA along the junction.
- Bullous pemphigoid: Usually linear IgG and/or C3 at the junction.



Continuous linear junctional IgA (linear IgA disease)

Serology supplements—but does not replace—DIF

- TG2 IgA and endomysial IgA support gluten-sensitive enteropathy.
- TG3 IgA can increase support for cutaneous disease.
- Negative blood tests do not automatically overturn convincing cutaneous DIF.

IgA anti-TG2: Celiac-related

IgA anti-TG3: DH-related

Total IgA: Assay interpretation

Supportive information; Interpret with DIF

Tissue transglutaminase IgA: Interpret the target

- Anti-TG2 IgA is a commonly used celiac-related serologic marker.
- Positivity supports gluten-associated autoimmunity.
- An isolated result is not a substitute for correct immunopathology.

IgA anti-TG2: Celiac-related

IgA anti-TG3: DH-related

Total IgA: Assay interpretation

Supportive information; Interpret with DIF

TG3 IgA: A disease-relevant serologic target

- Epidermal transglutaminase is the principal recognized DH autoantigen.
- Anti-TG3 assays may be helpful when conventional celiac serology is negative.
- Access and performance vary by testing platform.

IgA anti-TG2: Celiac-related

IgA anti-TG3: DH-related

Total IgA: Assay interpretation

Supportive information; Interpret with DIF

IgA status matters when interpreting serology

- An IgA-based assay may be misleading in IgA deficiency.
- Total serum IgA helps contextualize negative IgA antibody results.
- An appropriate IgG-based celiac testing strategy can be considered if deficient.

IgA anti-TG2: Celiac-related

IgA anti-TG3: DH-related

Total IgA: Assay interpretation

Supportive information; Interpret with DIF

HLA testing is an exclusion aid, not confirmation

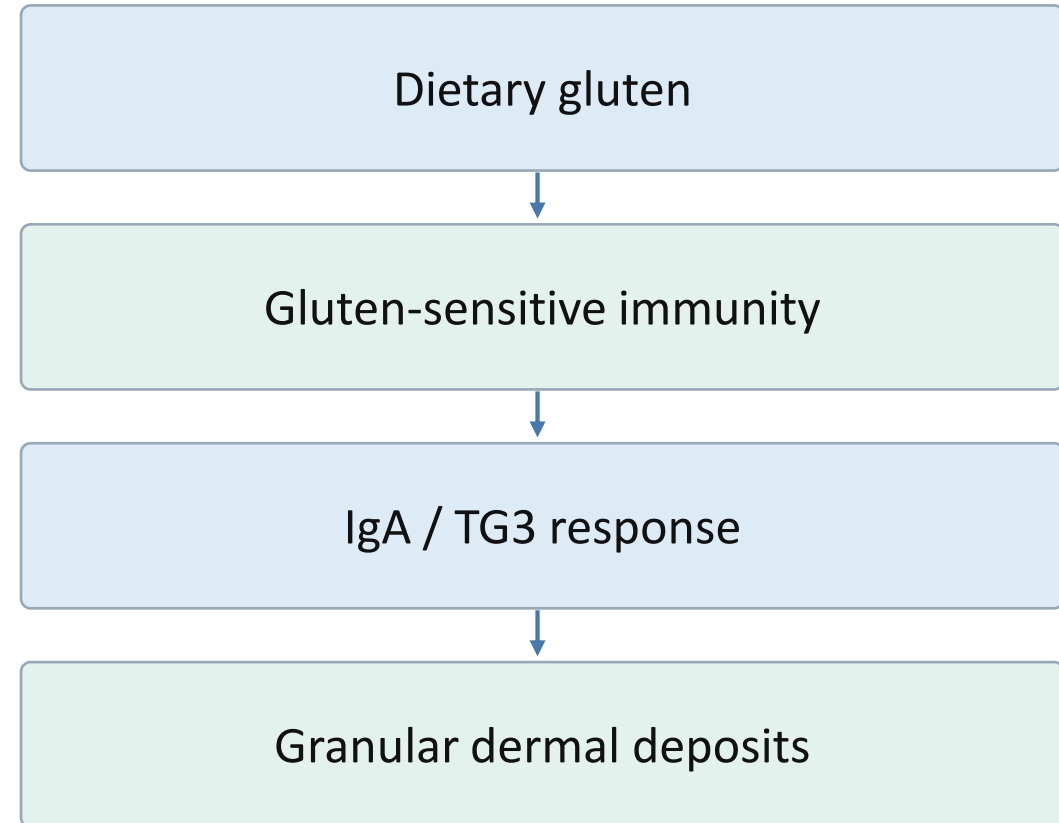
- HLA-DQ2 or DQ8 supports genetic susceptibility.
- A positive result is not disease-specific because these alleles are common.
- Testing is most useful when clinical, DIF, and serology results conflict.

INTERPRET IN CONTEXT

Clinical phenotype
+ immunopathology
+ supportive tests

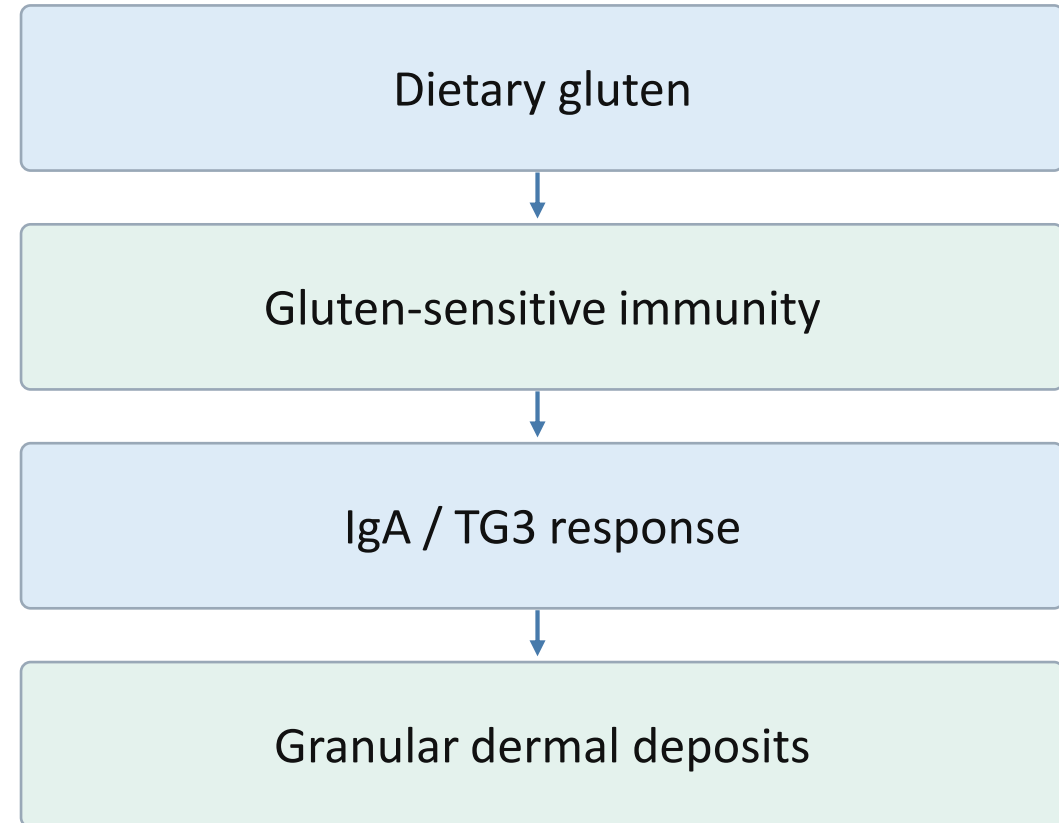
When is intestinal biopsy considered?

- Classic cutaneous DIF may already establish DH as a manifestation of celiac disease.
- Small-bowel biopsy is not mandatory solely to confirm established DH.
- Additional gastrointestinal indications require individualized assessment.



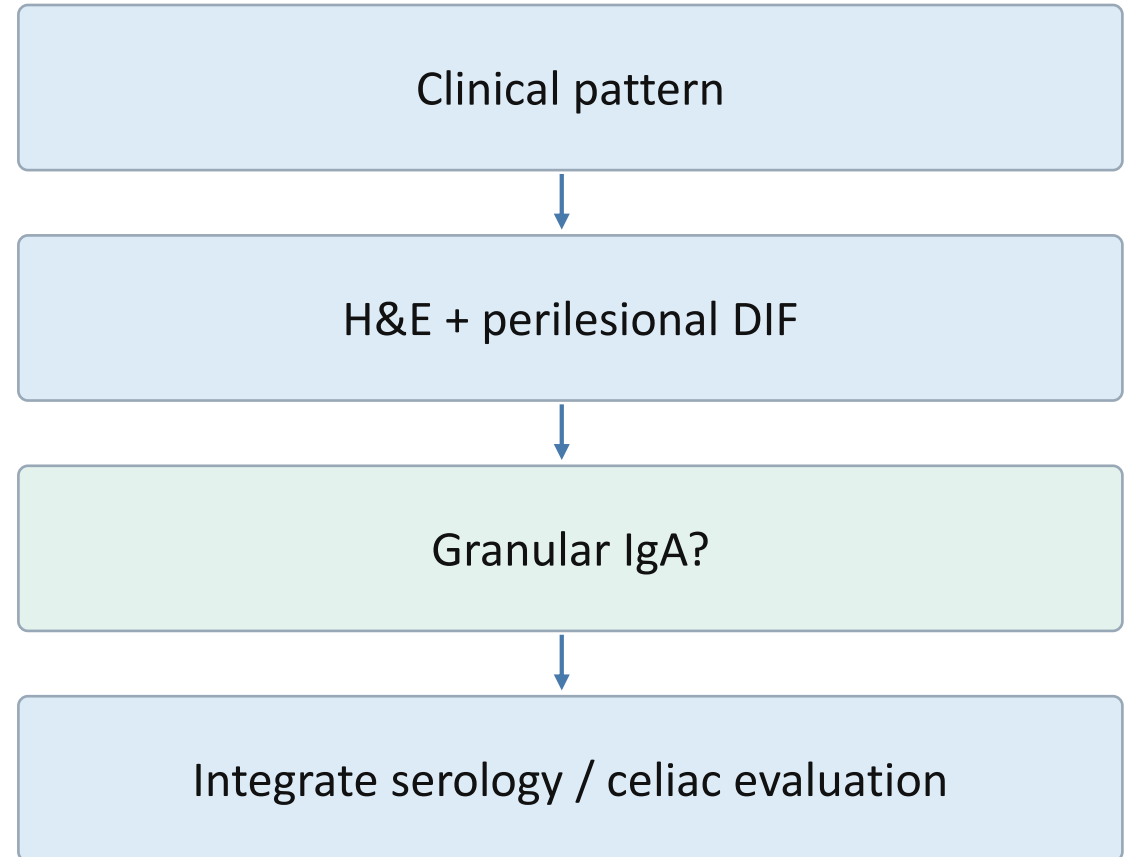
Assess associated enteropathy and its consequences

- Ask about bowel symptoms, nutritional status and anemia.
- Assess autoimmune comorbidity and intestinal complications as indicated.
- Coordinate care across dermatology, gastroenterology and nutrition.



A rational diagnostic pathway

- Recognize the patterned, highly pruritic eruption.
- Obtain lesional H&E and perilesional DIF using separate specimens.
- Interpret granular IgA with supported serology and celiac assessment.



Bullous pemphigoid: The nearest structural mimic

- Both DH and bullous pemphigoid can create subepidermal blisters.
- Bullous pemphigoid typically shows more eosinophils and a continuous linear junctional pattern.
- Pattern of immunoreactants is more discriminating than blister level alone.

DH

Papillary neutrophils

Granular IgA

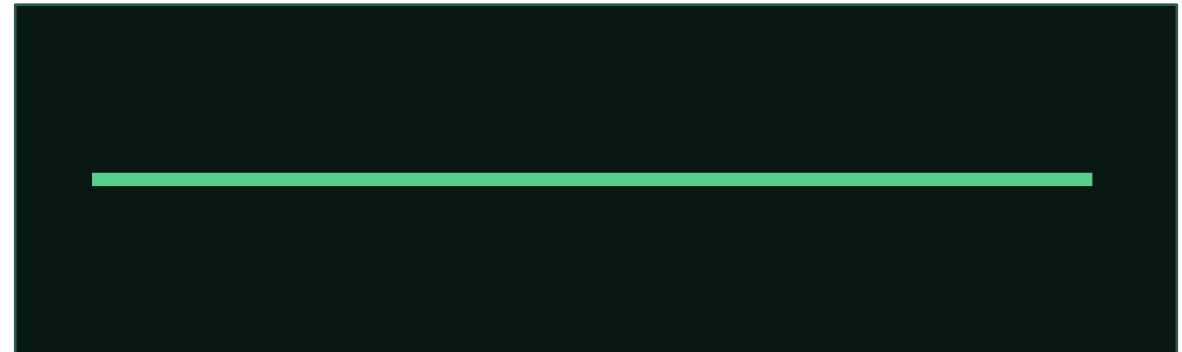
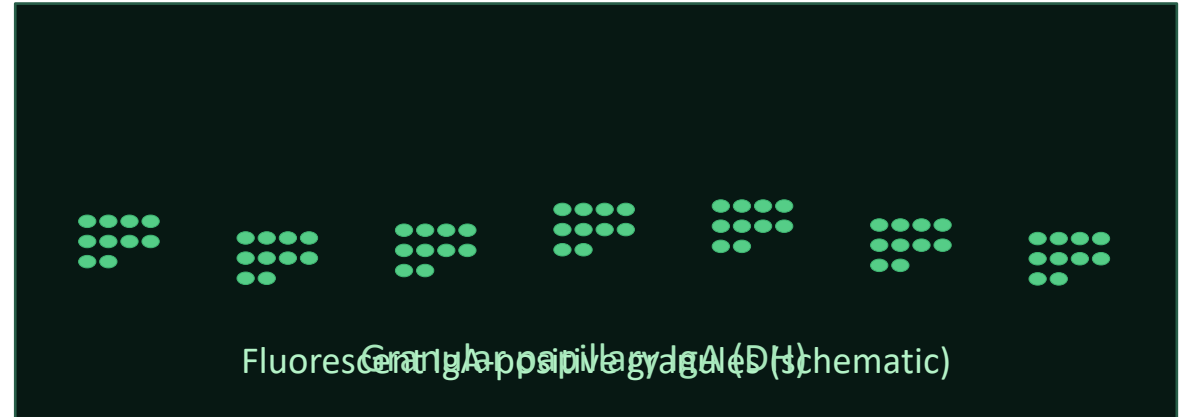
Bullous pemphigoid

Often eosinophils

Linear IgG / C3

Linear IgA bullous dermatosis: DIF distinguishes

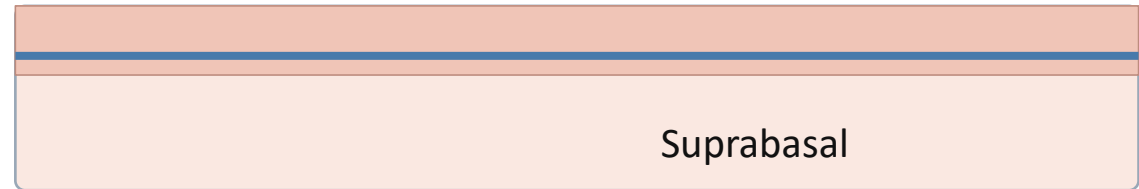
- Both may show neutrophils and subepidermal cleavage.
- Linear IgA disease demonstrates a smooth IgA line at the junction.
- DH classically shows granular IgA in dermal papillary tips.



Continuous linear junctional IgA (linear IgA disease)

Pemphigus: A different adhesion failure

- Pemphigus commonly exhibits intraepidermal acantholysis.
- Autoantibodies target desmosomal structures rather than papillary IgA complexes.
- The split level and DIF localization separate it from DH.



Common nonbullous mimics

- Eczema, scabies and prurigo can cause severe itch and excoriations.
- An absence of intact vesicles does not distinguish these from DH.
- Distribution, treatment history and selected investigations guide evaluation.

Pruritus is nonspecific

Symmetric extensor papulovesicles suggest DH

Definitive classification needs immunopathology

Other neutrophilic subepidermal blistering disorders

- Neutrophilic morphology is shared by several autoimmune dermatoses.
- Consider linear IgA disease and other rare interface blistering diseases.
- Definitive classification depends on DIF pattern and context.

DH

Papillary neutrophils

Granular IgA

Bullous pemphigoid

Often eosinophils

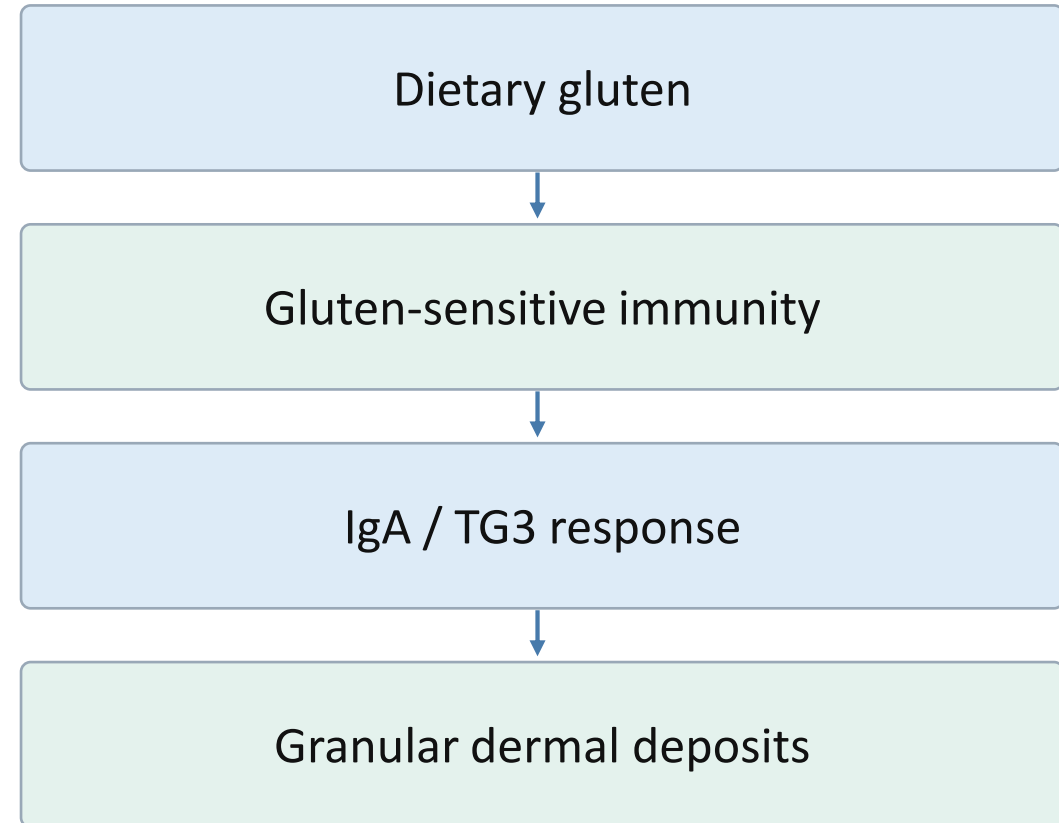
Linear IgG / C3

The diagnostic comparison in one table

Disease	Split	Main H&E clue	DIF
DH	Subepidermal	Papillary neutrophils	Granular IgA
Pemphigoid	Subepidermal	Often eosinophils	Linear IgG/C3
Linear IgA	Subepidermal	Often neutrophils	Linear IgA
Pemphigus	Intraepidermal	Acantholysis	Intercellular IgG

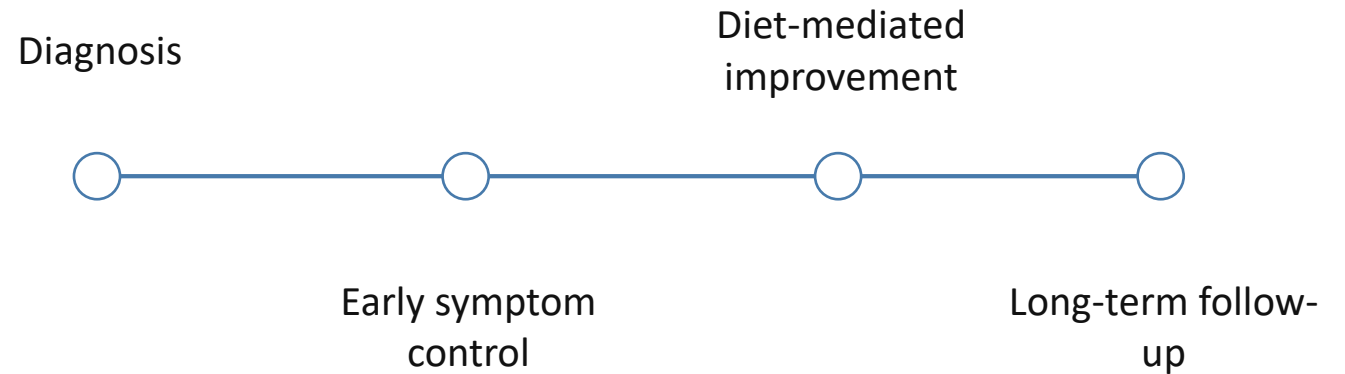
A gluten-free diet treats the driver

- Strict lifelong gluten avoidance is disease-modifying for skin and bowel disease.
- Resolution of the immunologic process can be slower than symptomatic treatment.
- Dietetic support helps maintain adherence and nutritional adequacy.



Diet response is not an immediate diagnostic test

- Skin improvement may take months; Full control can require a longer interval.
- DIF and some serologies become less informative after prolonged gluten avoidance.
- Do not delay diagnostic sampling in a patient still consuming gluten.



Dapsone provides rapid symptomatic control

- Dapsone can relieve pruritus and lesions while dietary treatment takes effect.
- It does not replace lifelong gluten avoidance.
- Treatment decisions require assessment of risks and monitoring.

Gluten-free diet: Underlying driver

Dapsone: Rapid symptom suppression

Both require appropriate follow-up

Dapsone: Monitoring is integral to prescribing

- Important risks include hemolysis and methemoglobinemia.
- Check relevant baseline measures, including G6PD status and blood counts, per local protocol.
- Ongoing monitoring includes blood counts and other safety tests as clinically indicated.

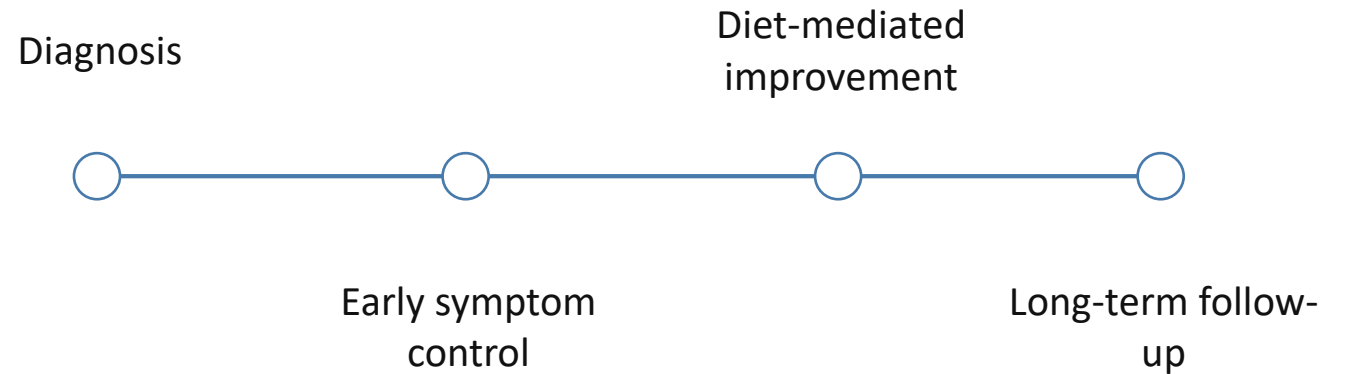
Gluten-free diet: Underlying driver

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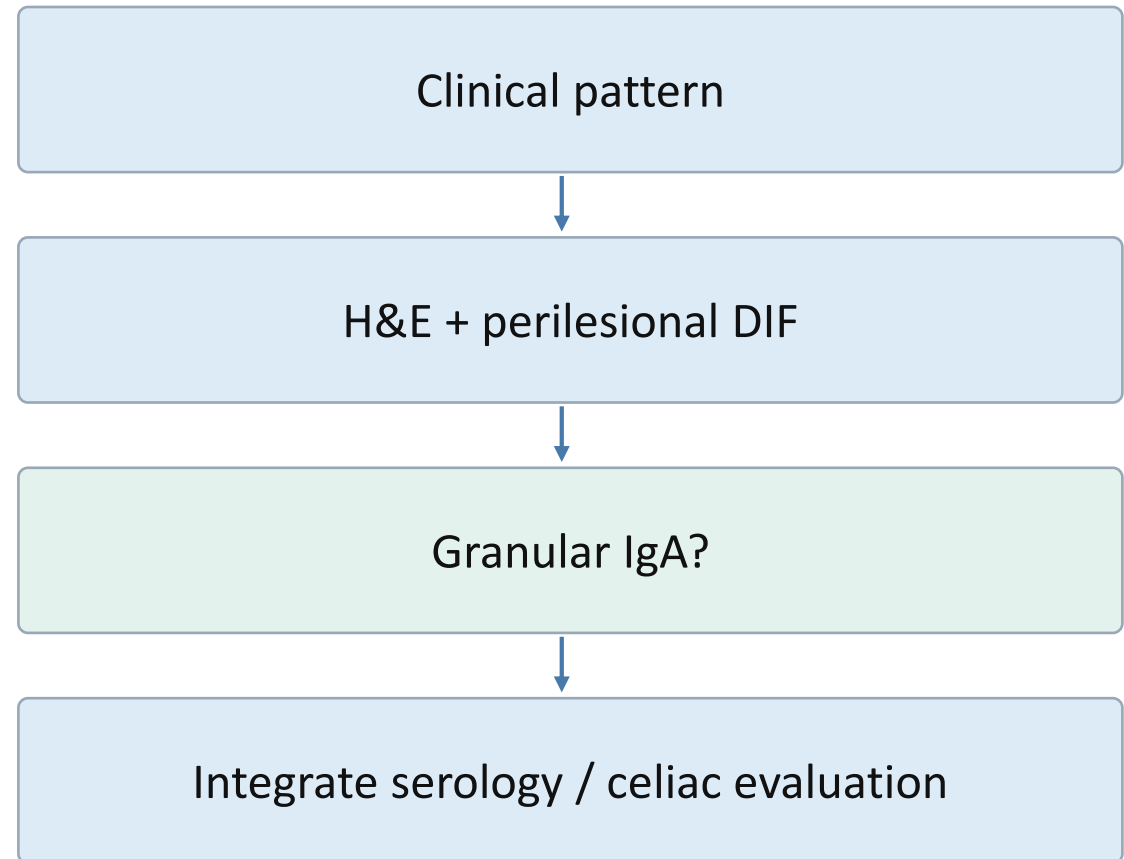
Follow-up combines cutaneous and systemic endpoints

- Document itch, active lesions and dapsons requirement.
- Review diet adherence, nutrition and evidence of enteropathy.
- Track indicated comorbidities rather than focusing on the rash alone.



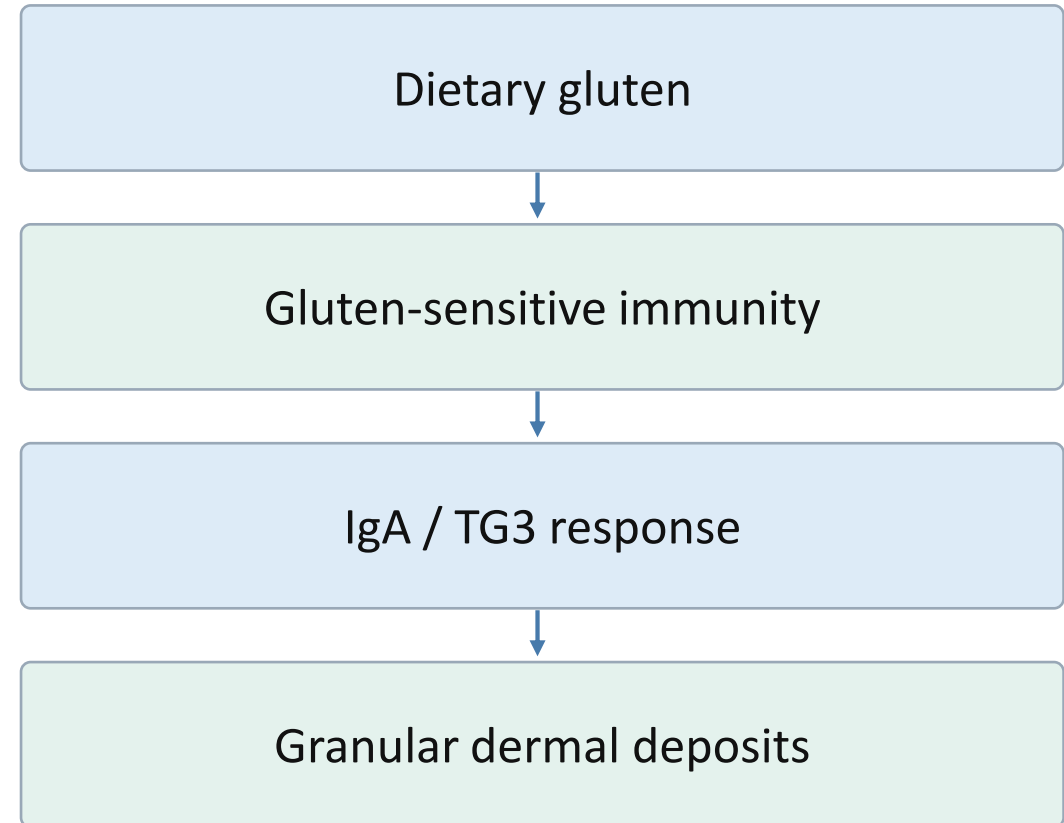
Persistent rash: Reassess the cause

- First consider inadvertent gluten exposure or imperfect dietary adherence.
- Reevaluate diagnosis if clinical or DIF findings were atypical.
- Assess treatment tolerance and alternative pruritic disorders.



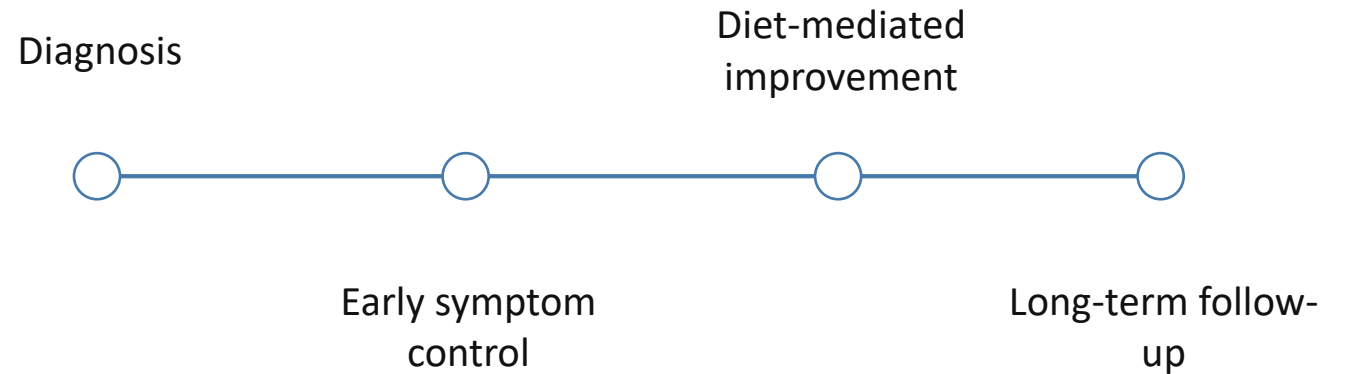
Associated conditions deserve clinical attention

- Celiac-associated nutritional abnormalities may accompany DH.
- Autoimmune thyroid disease is an established association.
- Long-term intestinal risk assessment belongs within celiac care.



Prognosis depends on sustained disease control

- Lifelong diet is the central long-term intervention.
- Medication needs often diminish when gluten avoidance is sustained.
- Multidisciplinary management supports durable clinical control.



Case: Symmetric excoriated plaques on the elbows

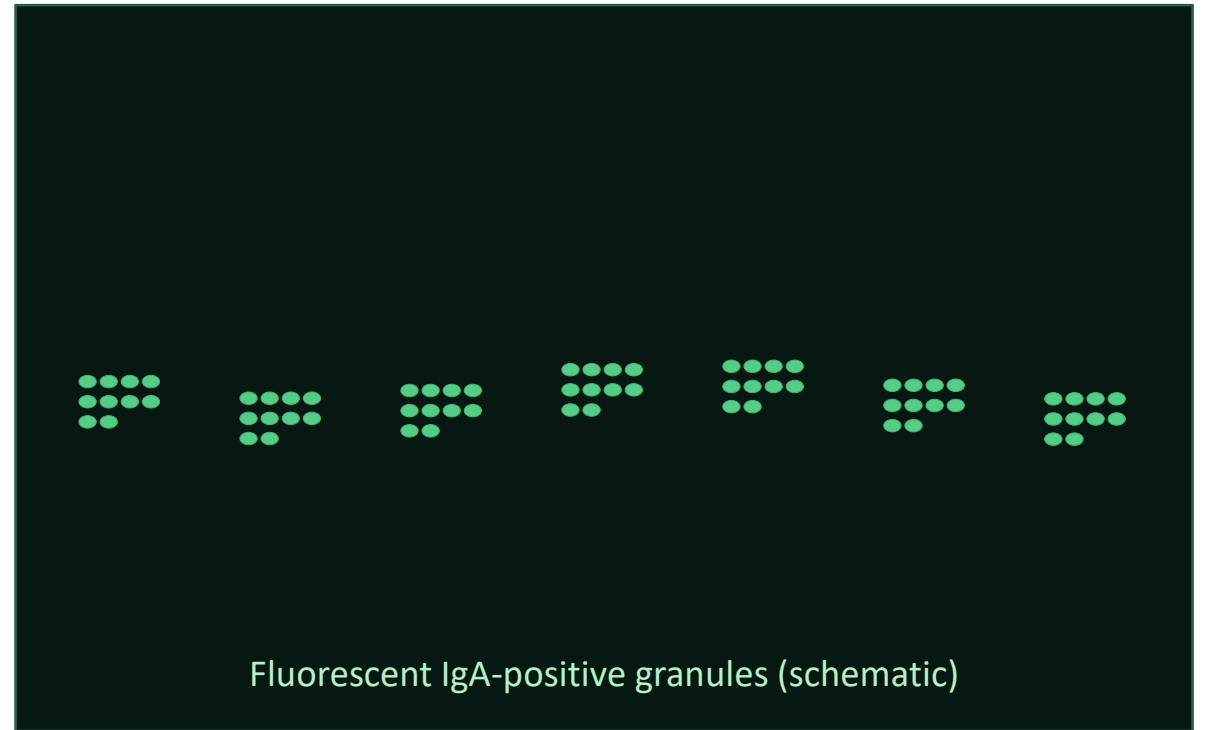
- An adult has severe itch, grouped erosions on both elbows and buttocks.
- Routine H&E reveals papillary-tip neutrophilic aggregates.
- What additional test most directly confirms suspected DH?

Clinical problem

Identify the most informative next diagnostic action and explain why.

Case answer: Biopsy adjacent normal skin for DIF

- Obtain perilesional clinically uninvolved skin for DIF.
- Look for granular IgA deposits at papillary dermal tips.
- A gluten-associated serologic assessment is supportive rather than a replacement.



Read the deposit pattern and its anatomic location

Case: Pruritus and negative serology

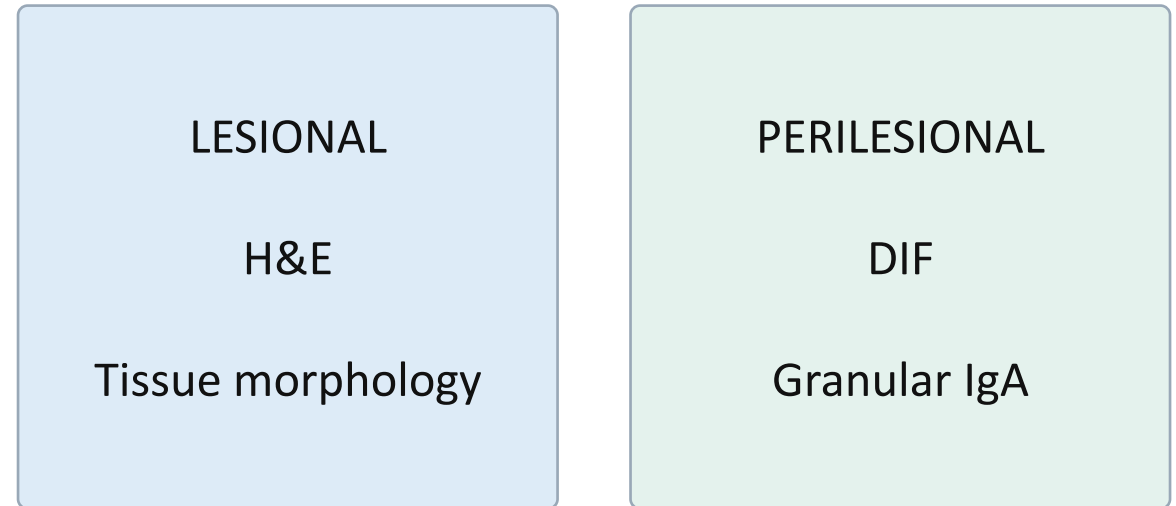
- A patient has classic distribution and an H&E-compatible lesion.
- Anti-TG2 IgA is negative; Biopsy for DIF came from an eroded vesicle.
- Which uncertainty should be resolved first?

Clinical problem

Identify the most informative next diagnostic action and explain why.

Case answer: Reassess sampling and IgA status

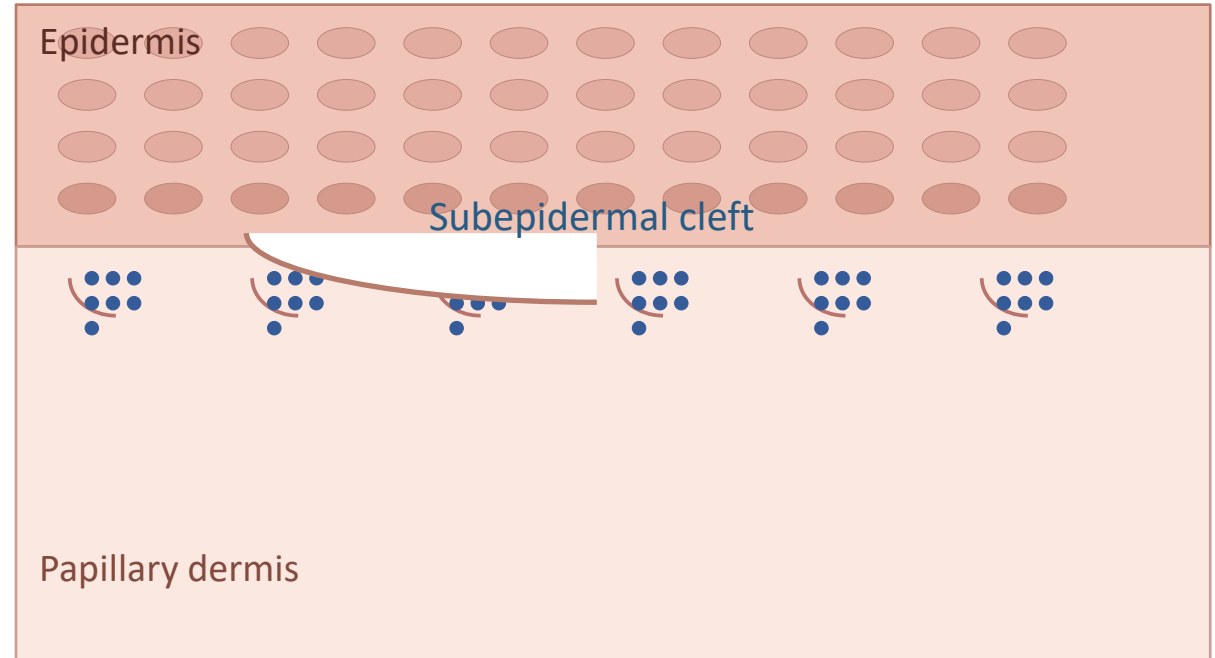
- An eroded blister is a suboptimal DIF specimen.
- Repeat properly sited DIF if clinical suspicion remains high.
- Consider total IgA and disease-relevant serology in context.



Separate biopsies • correct medium and site

Morphology application: Identify the primary lesion

- Papillary-tip neutrophils plus focal basal separation suggest early DH.
- An established cavity below the entire epidermis confirms the cleavage plane.
- Granular IgA distinguishes DH from several morphologic mimics.



Schematic — not a tissue specimen

Common interpretive errors

- Treating a negative lesional DIF sample as definitive exclusion.
- Confusing papillary granular IgA with a continuous linear junctional pattern.
- Assuming absent gastrointestinal symptoms means no celiac-related disease.

Sampling site can make DIF falsely negative

Granular $\neq$ linear IgA

Silent enteropathy remains relevant

Integrated clinicopathologic conclusion

Clinical pattern

H&E anatomy

Direct IF

Pruritic grouped extensor
eruption



Neutrophils at papillary tips



Granular papillary IgA

Key references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th ed.; Chapter 25.
- EADV S2k consensus guideline on DH (2021).
- Nguyen & Kim. Medicina (2021); Reunala et al. Am J Clin Dermatol (2021).
- NIDDK professional resource; Didona et al. review (2025).

Primary source
Robbins 11th edition

Supplementary references
EADV consensus • NIH • peer-reviewed reviews