# Acitretin therapy for Galli-Galli disease

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## INTRODUCTION

Galli-Galli disease (GGD) is a rare autosomal dominant genodermatosis, characterized by hyperkeratotic papules and progressive reticular hyperpigmentation involving the neck, trunk, and proximal extremities. GGD falls on a spectrum of reticulate hyperpigmentation disorders, and is thought to be an acantholytic variant of Dowling-Degos disease (DDD). No successful medicinal therapeutic approaches are reported in the literature. Here we describe a case of a severe flare of GGD successfully treated with acitretin.

## CASE REPORT

A 75-year-old white woman presented with a 40-year history of intermittent, widespread eruptions of pruritic crusted and scaling pink papules and tan macules, which started on the thighs and later progressed to involve the neck, trunk, flexor, and extensor surfaces of the extremities (Fig 1). Flares cleared with triamcinolone 0.1% ointment daily as needed. No scalp involvement or nail changes were noted. Medical history and prior medications were noncontributory. Family history was significant for a son with similar skin findings on the lower extremities.

Histopathology found epidermal acanthosis, suprabasal acantholysis, dyskeratosis, hypergranulosis, and hyperkeratosis with parakeratosis. Subsequent direct DNA sequencing was negative for a *KRT5* mutation; however, whole-exome sequencing found a heterozygous nonsense mutation in *POGLUT1*, p.(Arg218*); c.652>T.[1] Later, the same mutation was found in her symptomatic son but was absent in her 2 unaffected daughters. The constellation of clinical, histopathologic, and genetic findings supported a diagnosis of GGD.[2]

*Abbreviations used:*

DDD: Dowling-Degos disease
GGD: Galli-Galli disease

The patient, now 84 years old, recently presented for follow-up after an acute, severely pruritic eczematous eruption, thought to be secondary to a severe flare of GGD versus urticarial-phase bullous pemphigoid. The eruption spread to involve previously unaffected areas, including the face and scalp. The patient denied new medications, recent illness, fever, chills, changes in weight, or hospitalization. She denied use of any new topical agents. Physical examination found hundreds of excoriated and crusted 2- to 4-mm pink-to-violet papules diffusely over the posterior neck, back, chest, abdomen, bilateral arms, and legs. Many of the papules had overlying hemorrhagic crust. Laboratory examination found mild eosinophilia (6.4%; 0.5 K/mm$^3$). Immunofluorescent staining was negative from perilesional skin. Lesional skin biopsy found elongated rete ridges with subtle suprabasilar clefting and few dyskeratotic keratinocytes. A superficial, perivascular, predominantly lymphocytic infiltrate with eosinophils was also noted. The patient's clinical presentation and histopathology were consistent with a severe flare of GGD.

The eruption did not improve with a 14-day 40-mg prednisone taper, daily triamcinolone 0.1% ointment, and doxepin, 20 mg nightly, for symptomatic relief. Therefore, the patient was started on acitretin, 25 mg daily. After 1 month, the patient's skin findings and itch had significantly improved. Because of continued clinical improvement and some retinoid dermatitis on her arms, her regimen

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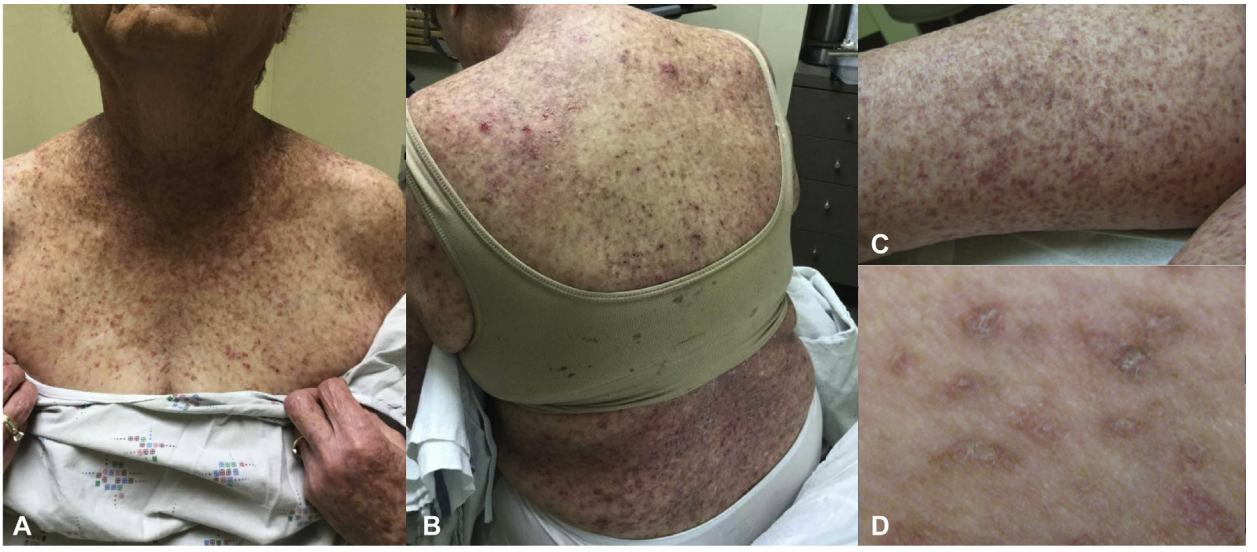


**Fig 1.** Initial presentation of GGD flare.

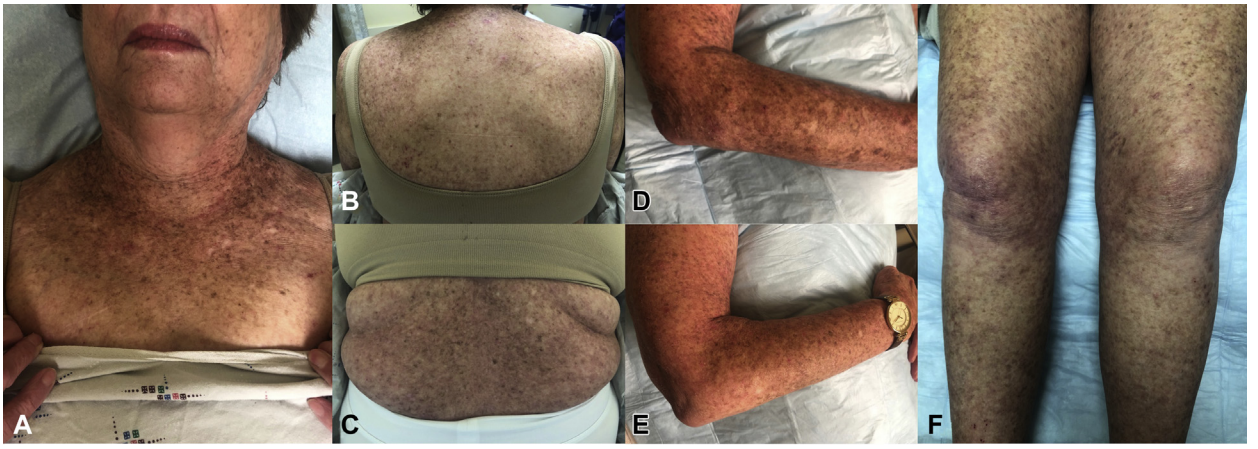


**Fig 2.** Clinical results following treatment with acitretin.

was tapered to acitretin, 10 mg daily. At her 10-month follow-up visit, the patient had no evidence of acute skin findings, and her itch had resolved with significantly improved sleep and quality of life. Skin examination was significant for chronic pigmentary changes, namely hundreds of red, purple, and brown, 2- to 4-mm macules over the proximal bilateral upper and lower extremities, chest, and back (Fig 2).

## DISCUSSION

GGD was first described in 1982 by Bardach et al[3] after 2 brothers, of the last name Galli, presented with hyperpigmented macules of the face and neck. GGD is an extremely rare autosomal dominant reticulate pigmentation disorder caused by mutations in *KRT5*, *POGLUT1*, and *POFUT1* genes.[1,4,5] Currently, there are fewer than 30 reported cases of GGD in the literature.

GGD presents between the second and seventh decade of life.[6] Common features include confluent, pink-to-brown hyperkeratotic papules that evolve into brown reticulate lentigo-like macules over the neck, trunk, flexor and extensor surfaces of the extremities.[7] The clinical differential diagnosis includes Darier disease, Grover disease, and disorders of reticulate hyperpigmentation. Family history, distribution of reticulate pigmentation, and other associated examination findings help differentiate these entities.

The distinguishing histologic features of GGD include suprabasilar acantholysis and lentiginous changes. Dyskeratosis is present in some cases. The histologic differential diagnosis for GGD includes entities characterized by focal acantholysis, namely

**Table I.** Reported response to treatments attempted for GGD

| Study | Patient age/sex | Clinical morphology | Suprabasal acantholysis | Lentiginous changes | Dyskeratosis | Genetic testing | Treatment (response) |
|---|---|---|---|---|---|---|---|
| Braun-Falco et al (2001)[8] | 53/M | Brown pigmentation in skin folds with chronic pruritic papular eruption of neck, axilla, lateral trunk, dorsal hands, groin | + | + | - | NT | Tretinoin 0.03% and urea 12% creams (pruritus worsened, irritation)<br>Ultraviolet B phototherapy (slight antipruritic and stabilizing effect)<br>Systemic and topical corticosteroids (short-term partial improvement) |
| Cooper et al (2004)[9]* | 42/F | Pruritic, erythematous scaly papules and vesicles and lentigines of forehead, upper back, chest, and lower extremities | + | + | + | (-) *ATP2A2* | Emollients (pruritus controlled) |
| Cooper et al (2004)[9]* | 39/F | Erythematous papules and tan lentigines of extremities, trunk, and neck | + | - | - | (-) *ATP2A2* | Topical retinoids (no improvement) |
| El Shabrawi-Caelen et al (2007)[7] | 65/F | Recurrent pruritic erythematous and brown macules and papules, some with scale over trunk, flexural and extensor lower extremities | + | + | + | NT | Topical corticosteroids (no improvement)<br>Topical retinoids (no improvement) |
| El Shabrawi-Caelen et al (2007)[7] | 67/F | Pruritic erythematous and lentigo-like macules of inframammary skin, lower extremities | + | + | - | NT | Topical and oral corticosteroids (incomplete resolution)<br>Topical and oral retinoids (incomplete resolution)<br>Ultraviolet B phototherapy (incomplete resolution) |
| Gilchrist et al (2008)[6] | 41/M | Confluent pink and tan macules and papules, reticular hyperpigmentation of neck, chest, back, proximal extremities | + | + | - | NT | Prednisone and cyclosporine (pruritus improved, eruption persisted) |
| Gomes et al (2011)[10] | 67/F | Recurrent pruritic erythematous hyperkeratotic papules and brown macules of extensor and flexural surfaces, dorsal hands, neck, trunk | + | + | + | NT | Topical corticosteroids (no improvement)<br>Acitretin, 25 mg/d (short-term partial improvement) |
| Müller et al (2008)[11] | 52/M | Brown reticulate macules of flexures, neck, groin, and trunk | + | + | - | NT | Topical corticosteroids (short-term improvement) |
| Müller et al (2008)[11] | 25/M | Pruritic papules, brown macules of trunk, neck, flexures, axillae, inguinal folds, hands, acneiform papules of back, neck, and face | + | + | - | NT | Topical corticosteroids (no improvement) |

Continued

**Table I.** Cont'd

| Study | Patient age/sex | Clinical morphology | Suprabasal acantholysis | Lentiginous changes | Dyskeratosis | Genetic testing | Treatment (response) |
|---|---|---|---|---|---|---|---|
| Voth et al (2011)[13] | 68/M | Chronic pruritic erythematous hyperkeratotic papules of axillae, neck, trunk, and groin | + | + | - | c.418dupA *KRT5* gene | Topical corticosteroids (no improvement)<br>Topical antibiotics (no improvement)<br>Oral antihistamines (no improvement)<br>Erbium:YAG laser (dyspigmentation, resolution of symptoms) |
| Desai et al (2016)[12] | 55/F | Hyperpigmented reticulated macules of neck, chest, abdomen, extensor and flexor surfaces of upper and lower extremities | + | + | - | NT | Topical retinoids (no response reported) |
| Dupuy et al (2018)[14] | 58/F | Hyperkeratotic, red-brown flat-topped papules with background of lentigo-like macules on trunk, upper and lower extremities | + | + | + | NT | Acitretin (improved rash, discontinued due to hair loss)<br>Triamcinolone 0.1% cream (pruritus and erythema improved)<br>Isotretinoin, 30-40 mg/d (pruritus and erythema improved, discontinued due to "blistering" skin reaction) |
| Lőrincz et al (2018)[15] | 74/M | Hypopigmented papules, hyperpigmented macules of neck, trunk, and flexor extremities | + | + | - | c.418dupA *KRT5* gene | Acitretin, 25 mg every other day to daily (inflammatory eruption and pigmentation improved) |
| Current case | 84/F | Pruritic crusted and scaling pink papules and tan macules of trunk, neck, flexor and extensor extremities | + | + | + | c.652>T *POGLUT1* gene | Prednisone, 40 mg (no improvement)<br>Topical corticosteroids (no improvement)<br>Doxepin, 20 mg nightly (no improvement)<br>Acitretin, 10-25 mg/d (pruritus and papular eruption resolved) |

*NT*, Not tested.
*Authors hypothesized diagnosis of widespread Grover disease with lentiginous changes.

Darier disease, Hailey-Hailey disease, and Grover disease. The combination of suprabasilar acantholysis and lentiginous changes on histology is helpful in differentiating GGD.

Treatment of GGD is difficult, and most published cases report incomplete or temporary response to therapy or do not comment on treatment. Case reports that report both treatment and response are documented in Table I.[8-12] Only one other report exists of sustained treatment response to GGD. Voth et al[13] describe a 68-year-old man who experienced sustained resolution of his symptoms at 12-month follow-up after 2 treatments with erbium: Yttrium-Aluminum Garnet (YAG) laser.[13] After treatment, the authors noted scar formation, hyperpigmentation, and depigmentation of the treated skin. Lasers may provide a promising therapeutic option for some patients; however, they are associated with risk of dyspigmentation and scarring and are less widely available and more costly than other medical treatments. Our literature search found 3 patients who were treated with acitretin.[10,14,15] All 3 patients experienced variable positive responses to acitretin; however, none experienced sustained resolution of symptoms, and one patient discontinued treatment because of hair loss. Other therapies, including topical retinoids, isotretinoin, ultraviolet B phototherapy, topical and oral corticosteroids, and antihistamines yielded variable results, ranging from worsening of symptoms to partial improvement. Despite a variety of potential therapeutic options published in the literature, there is only one other report of sustained resolution of symptoms with treatment and no cases addressing treatment of a GGD flare, a feature not widely described in the literature.

## CONCLUSION

GGD is a rare genodermatosis that is considered an acantholytic variant of DDD and is associated with autosomal dominant mutations in *KRT5*, *POGLUT1*, and *POFUT1* genes. Clinically, GGD presents with red-to-brown hyperkeratotic papules that evolve into brown reticulate lentigo-like macules over the trunk, neck, flexor, and extensor surfaces of the extremities. In rare instances (as with our patient), severe flares and a more diffuse distribution of cutaneous involvement may be appreciated. Histopathologically, GGD is characterized by the combination of suprabasilar acantholysis and lentiginous changes. Although GGD remains difficult to treat, future patients may benefit from treatment with acitretin.

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