Corneal Transplant Related Galli-Galli Disease

John C. Affeldt M.D.

Associate Professor
Loma Linda University Eye Institute

Assistant Clinical Professor
USC Roski Eye Institute / Keck School of Medicine of USC

Board of Directors / Professional Association
Doheny Eye Institute / UCLA

Galli-Galli Disease (GGD)

- Very rare autosomal dominant *genodermatosis* (~27 reported cases)
- Member broader family of *reticulated pigmented skin disorders*
  - Galli-Galli disease (GGD)
  - Dowling-Degos disease (DDD)
  - Reticulate acropigmentation of Kitamura
  - Reticulate acropigmentation of Dohi
  - Haber Syndrome

Galli - Galli Disease (GGD)

- First described by Bardach in 1982
- Identified in two brothers named *Galli*
- Presented with a reticulated hyperpigmented skin eruption affecting skin folds

Galli - Galli Disease (GGD)

- Initially thought to represent a distinct clinical entity
  - Clinical presentation indistinguishable from DDD
  - Consistent histopathology finding of *acantholysis* which was unique to GGD

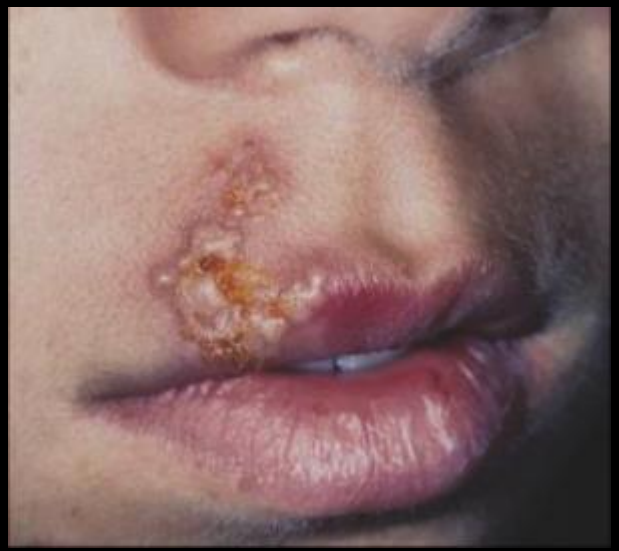
Acantholysis

- Loss of connection between epidermal keratinocytes secondary to breakdown of desmosomal intercellular attachments

Note the rounded and detached, free floating keratinocytes

Acantholysis

- Characteristic of various skin conditions including;
  - Galli-Galli Disease
  - Pemphigus vulgaris
  - Herpes virus vesicular eruptions

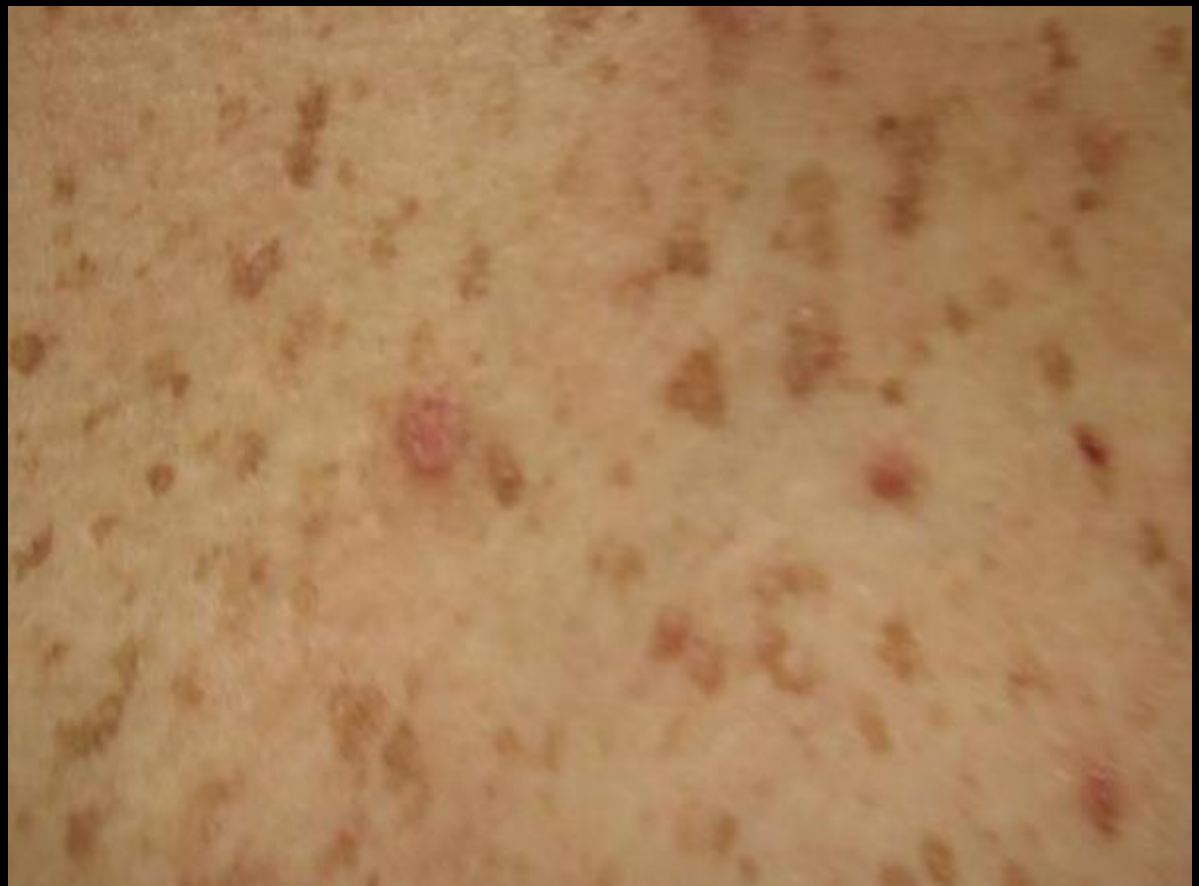


Galli - Galli Disease (GGD)

- Subsequent research identified common genetic defect for both GGD and DDD
- Identical frameshift and nonsense mutations located on KRT5 gene
- Consequently GGD now considered an *acantholytic variant* of Dowling-Degos Disease

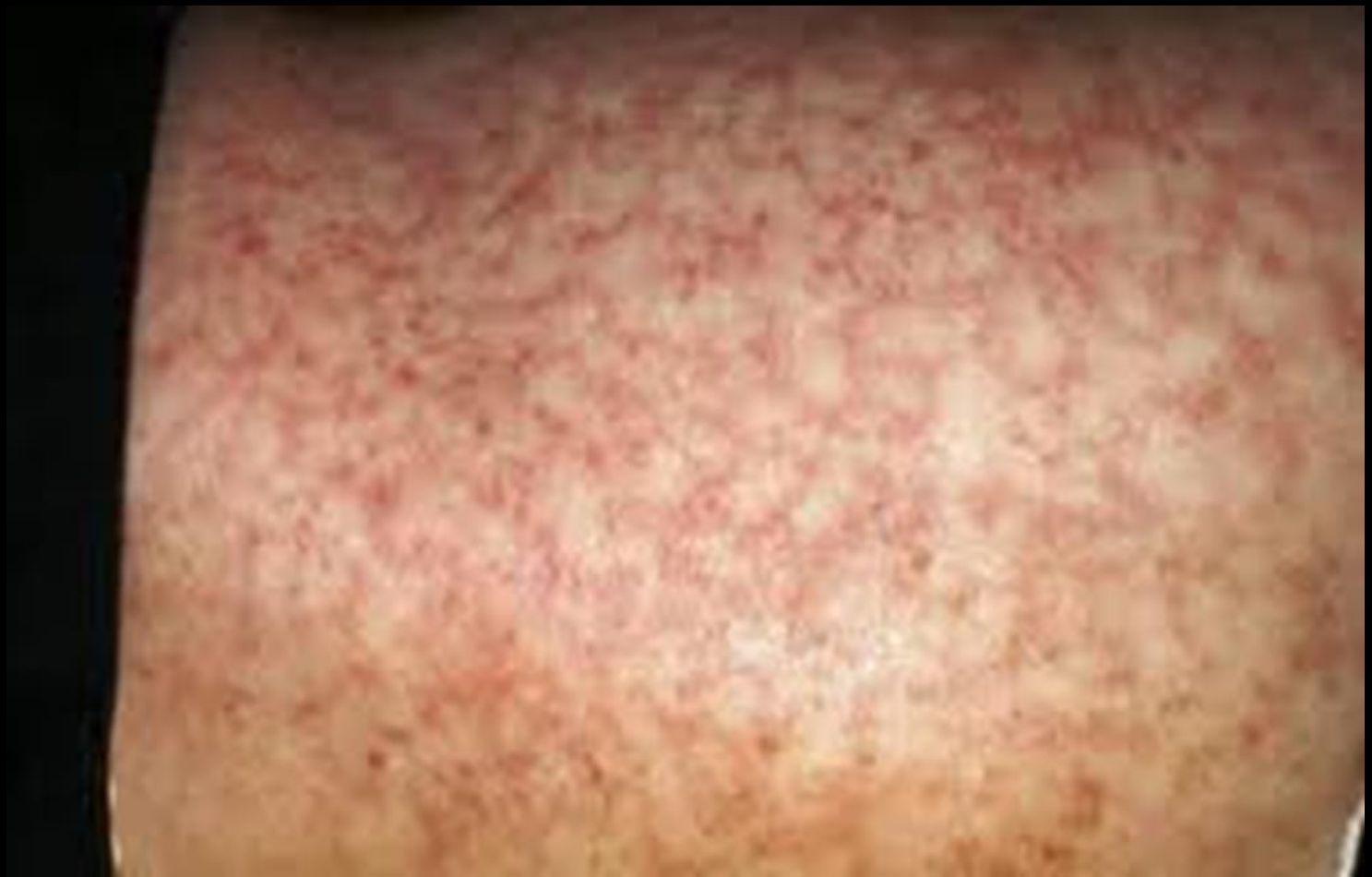
Clinical Presentation GGD

- Multiple 1-2 mm red - dark brown puritic papules



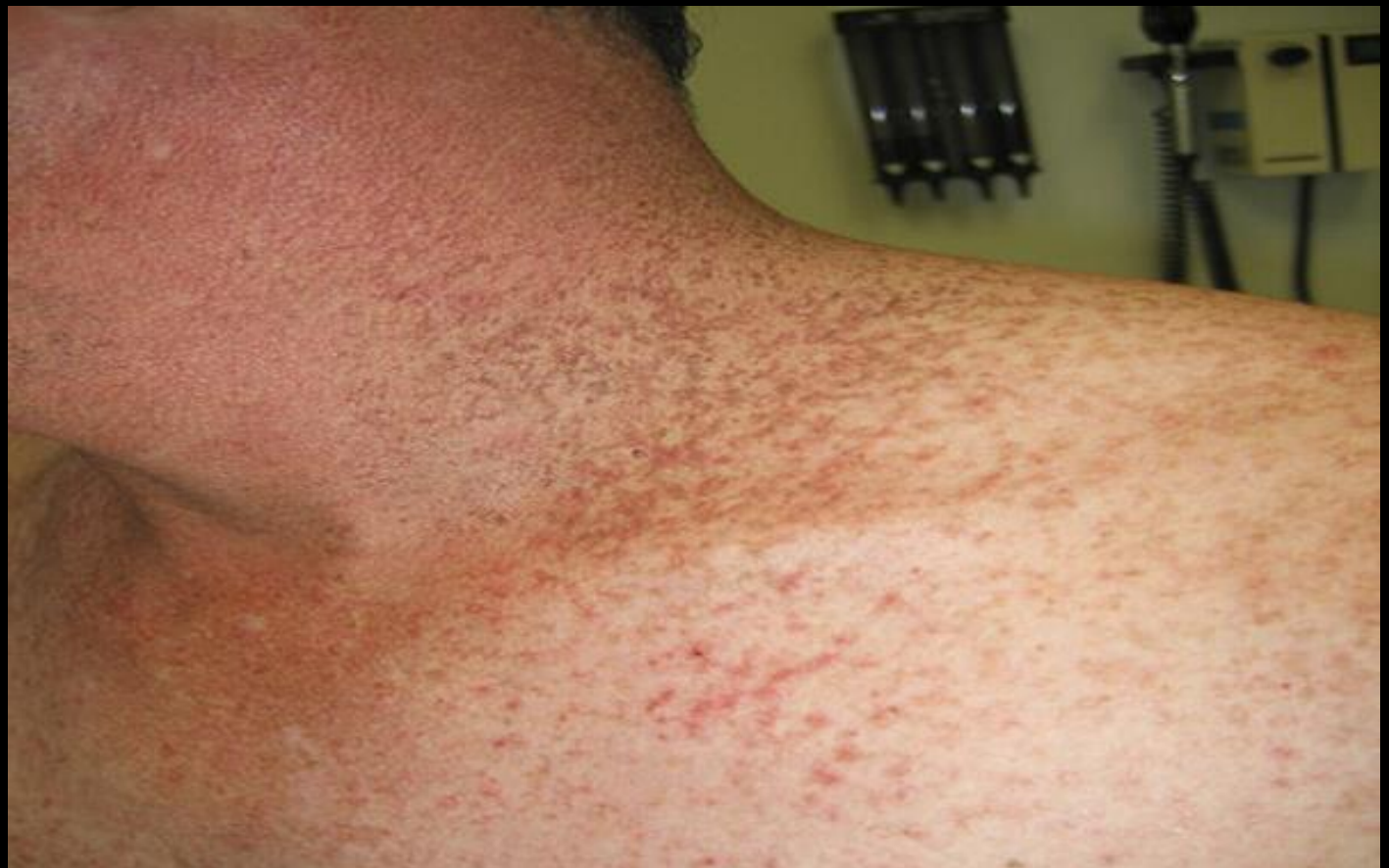
Clinical Presentation GGD

- Focally confluent in a reticulated (net-like/chicken wire) pattern



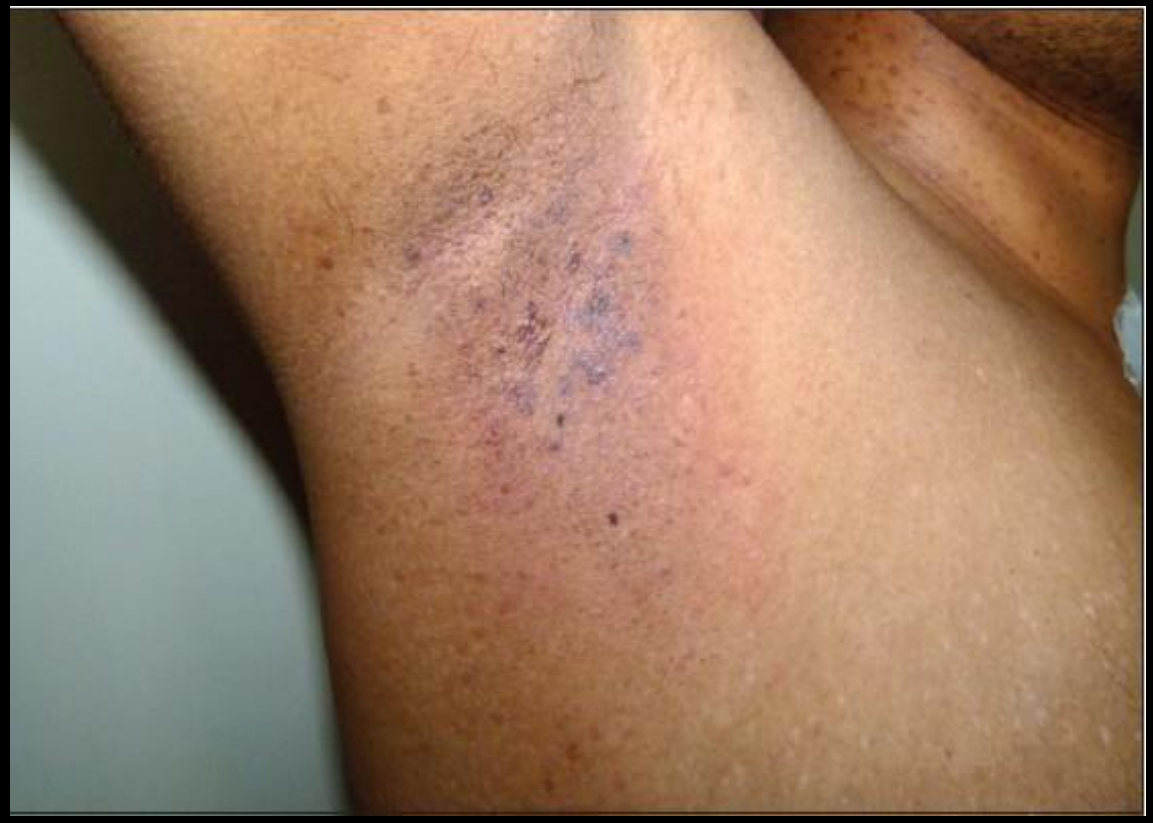
Clinical Presentation GGD

- Predilection for *flexural* (skin fold) areas including the *neck*



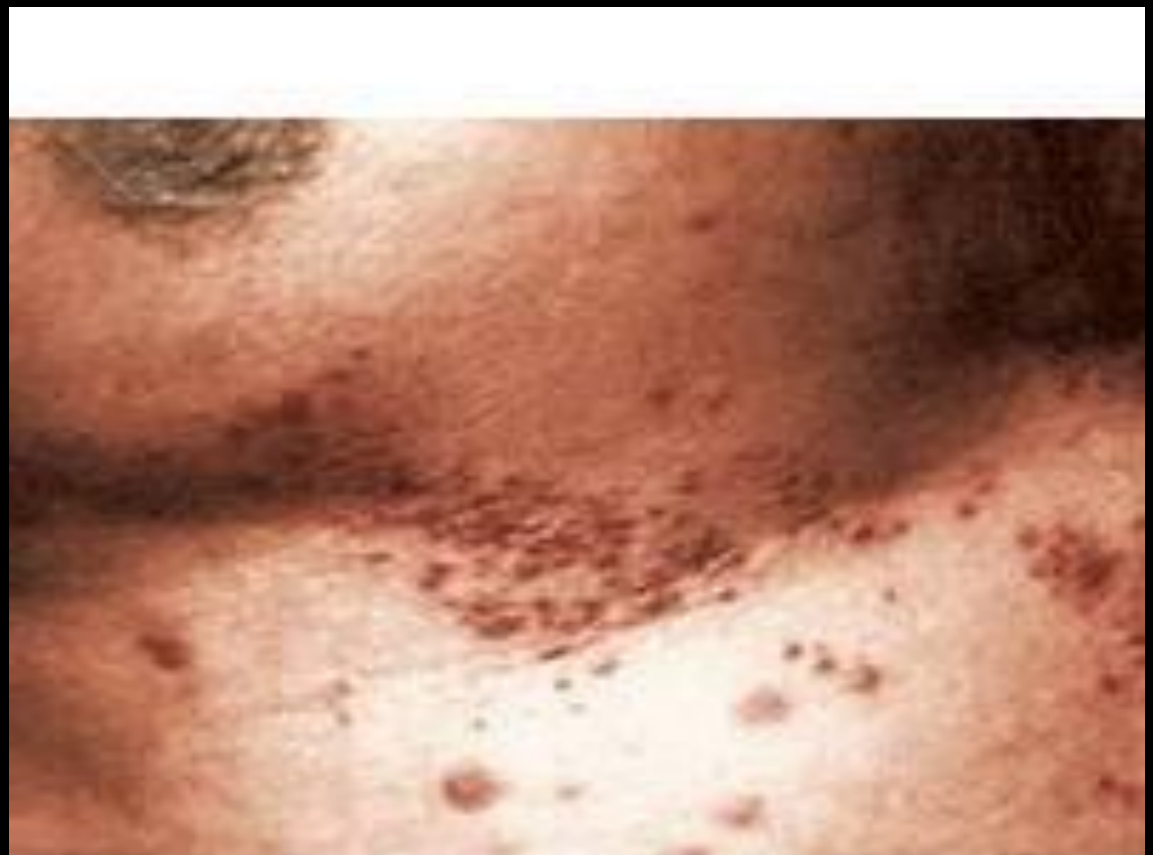
Clinical Presentation GGD

- Predilection for *flexural* (skin fold) areas including the *axilla*



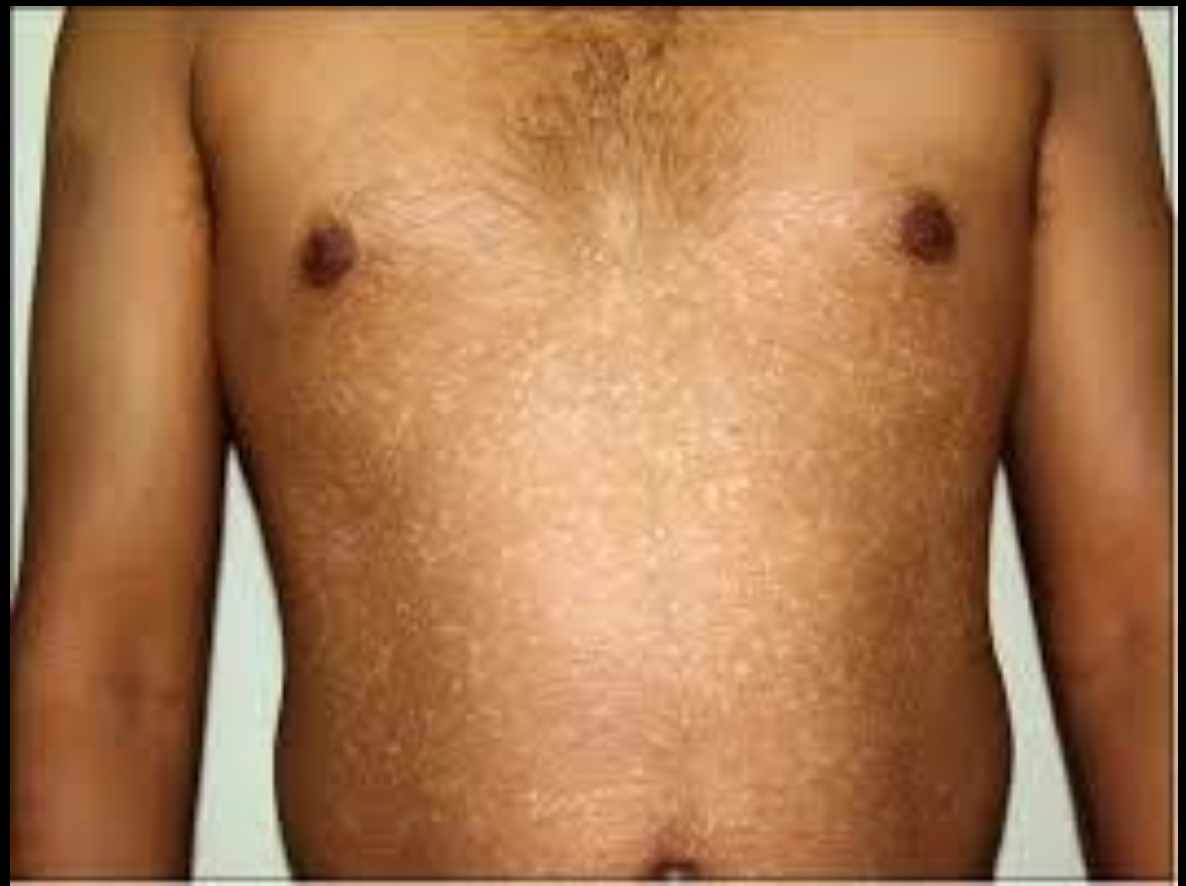
Clinical Presentation GGD

- Predilection for *flexural* (skin fold) areas including the *inframammary* and inguinal regions



Variant Manifestations GGD

- Grover disease-like erythematous, keratotic papules and lentigo-like macules of the trunk and extremities

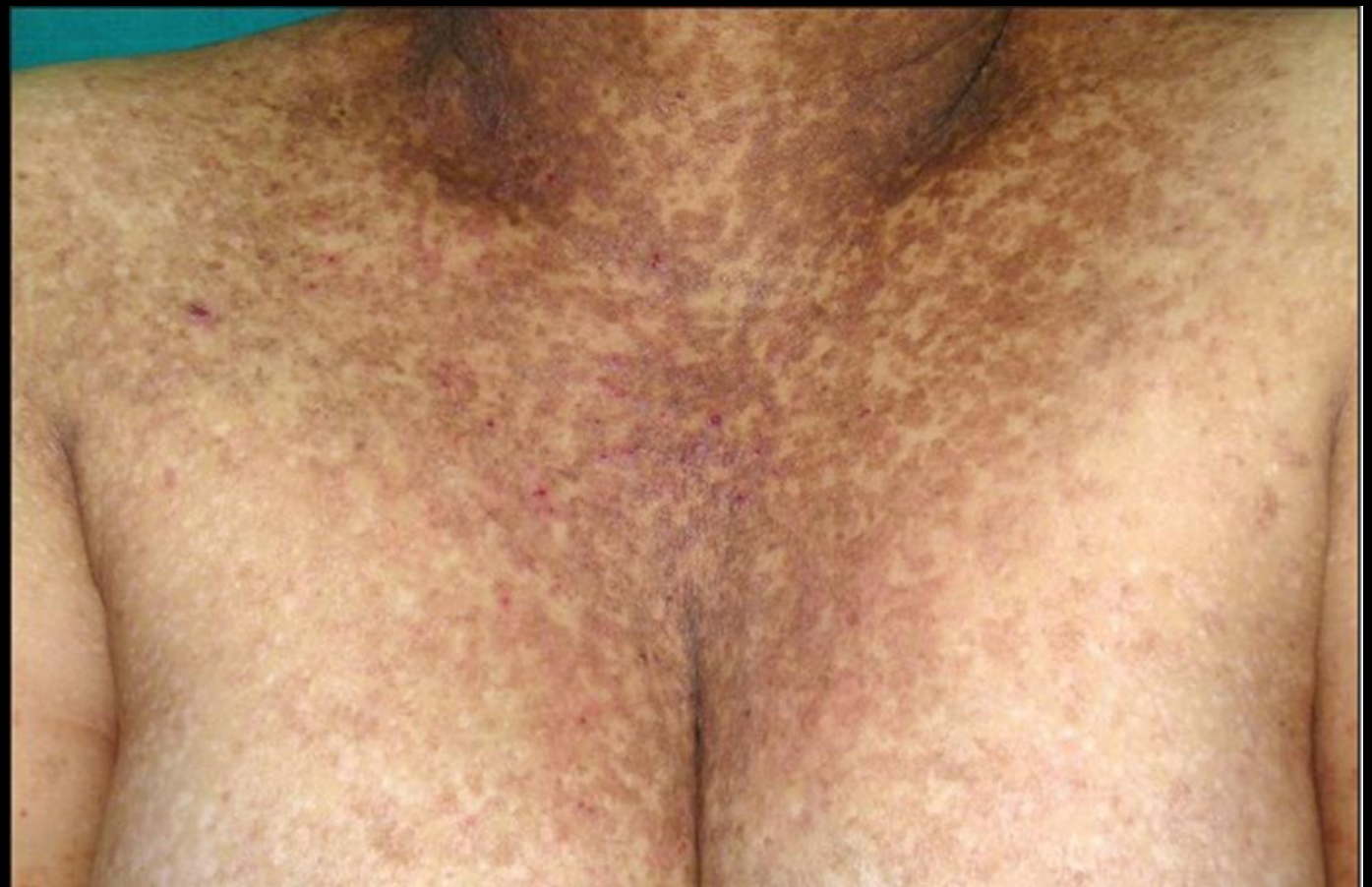


Variant Manifestations GGD

- Grover disease-like erythematous, keratotic papules and lentigo-like macules of the trunk and extremities

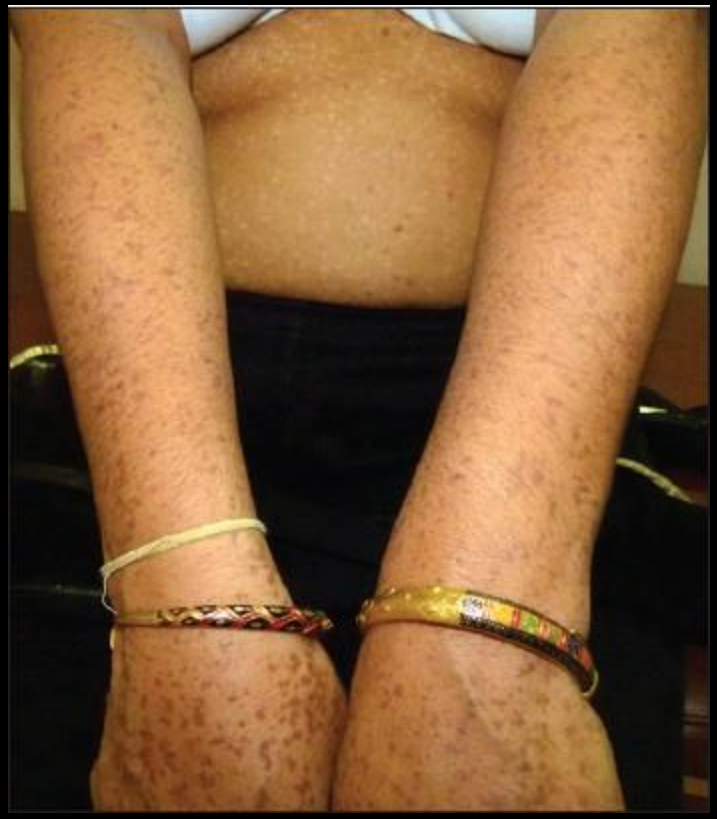
Variant Manifestations GGD

- Grover disease-like erythematous, keratotic papules and lentigo-like macules of the trunk and extremities



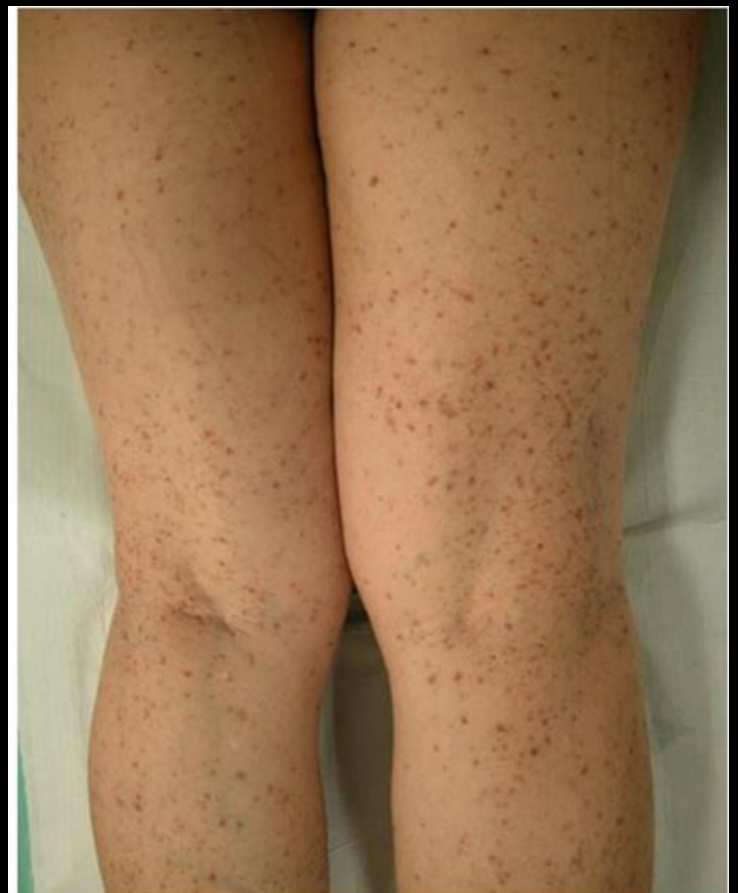
Variant Manifestations GGD

- Grover disease-like erythematous, keratotic papules and lentigo-like macules of the trunk and extremities



Variant Manifestations GGD

- Grover disease-like erythematous, keratotic papules and lentigo-like macules of the trunk and extremities

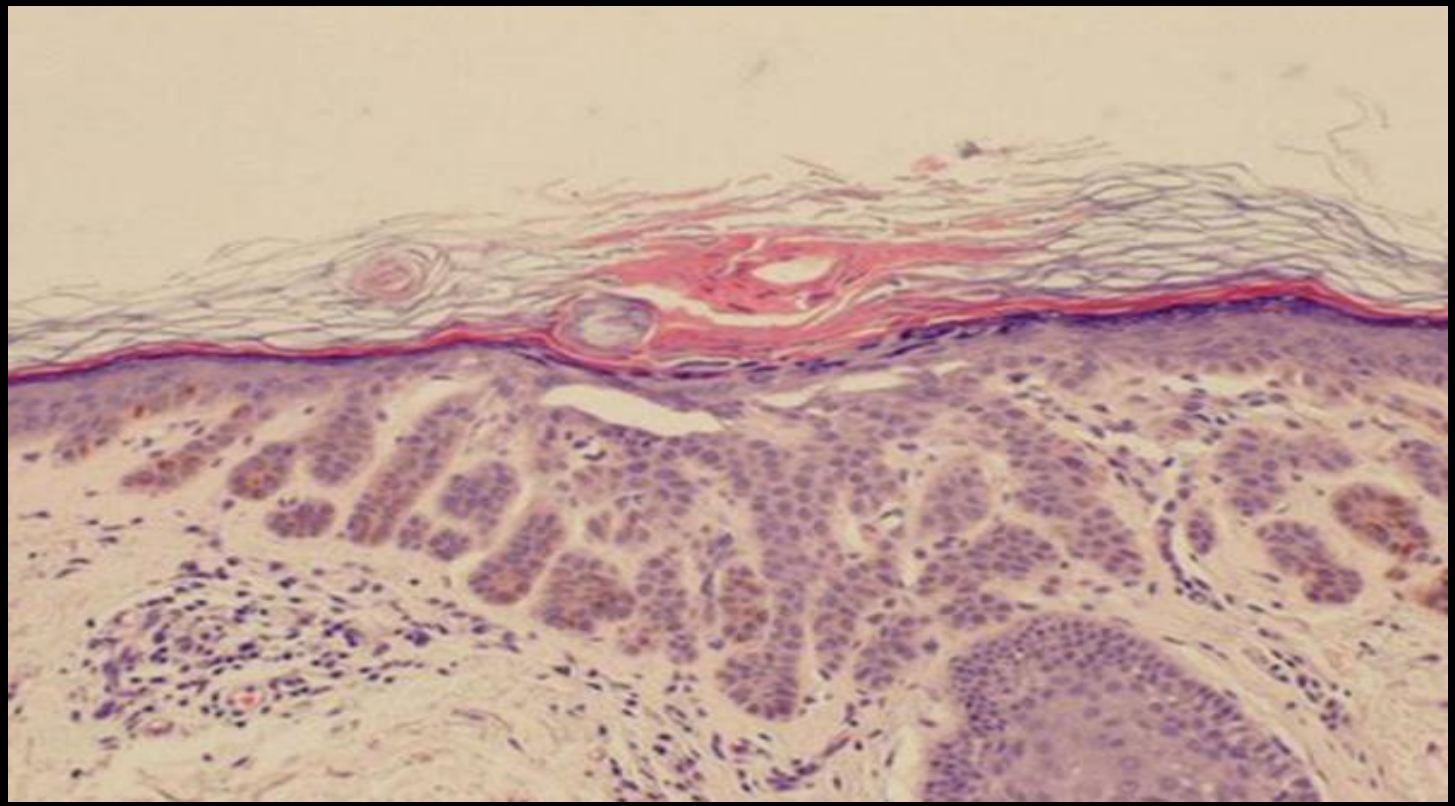


GGD Disease Characteristics

- Age at onset varies widely: teens – 70's
- Inheritance pattern:
  - Autosomal dominant with incomplete penetrance
  - Sporadic
- Disease is progressive without spontaneous remission

Histopathology

- Digitiform elongation of the rete ridges
- Basal layer hyperpigmentation
- Focal suprabasal acantholysis (hallmark feature)



Association With Immune Suppression

Association with Immune Suppression

- Grover's Disease
  - *Transient* (weeks-months) acantholytic dermatosis of unknown cause
  - Manifests as a papular skin eruption on trunk and proximal extremities
  - Clinically similar to and high on the differential dx list for GGD

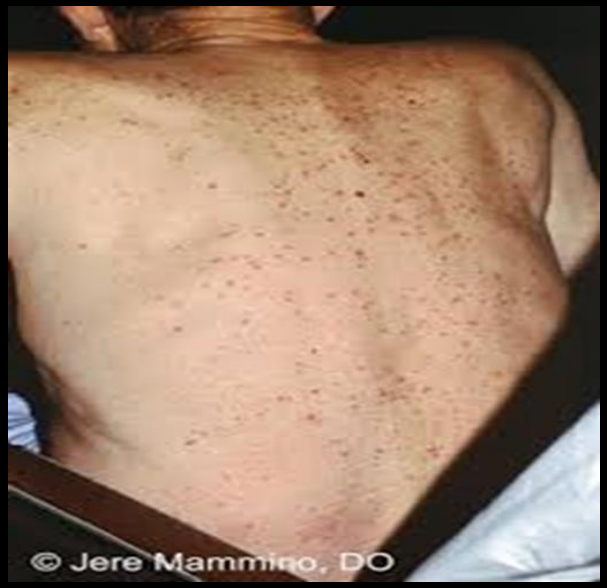
Association with Immune Suppression

- Grover's Disease has a well documented association with immunosuppressive conditions including;
  - HIV
  - Hematologic malignancies
  - Bone-marrow allotransplantation (1.8% incidence)
  - Renal transplantation (solid organ)

(1) Breustedt W, et al. *Transitory acantholysis (Grover) in an HIV infected patient*. Z Hautkr 1990; 754-756. (in German)
(2) Landra N, et al. *Transient acantholytic dermatosis (Grovers disease): A review of 73 cases* (Abstract). 18th world Congress of Dermatology, New York 1992; June 12-18, p. 129A.
(3) Horn T, et al. *Transient acantholytic dermatosis in immunocomprised febrile patients with cancer.* Arch Dermatol 1987: 122: 238-240.
(4) Guana A, et al. *Transient acanthlytic dermatosis in oncology patients.* J Clin Oncol 1994; 12:1703-1709.
(5) Manteaux A, et al. *Transient acantholytic dermatosis in patients with cancer.* Cutis 1990; 46; 488-490. ; 77; 245-246.
(6) De Argila D, et al. *Grover's disease in a patient with gastric carcinoma.* Acta Derm Venereol 1997
(7) Roger M, et al. *Grover's disease associated with Waldenstrom's macroglobulinemia and neutrophilic dermatosis.* Acta Derm Venereol 2000; 80; 145-146.
(8) Harvell J, et al. *Grover's-like disease in the setting of bone marroee transplantation and autologous peripherial blood stem cell infusion.* Am J Dermatopathol 1998; 20: 179-184.
(9) Bayer-Garner I, et al. *The spectrum of cutaneous diseases in multiple myeloma.* J Am Acad Dermatol 2003: 48: 497-507.
(10) Zelickson B, et al. *Transient acantholytic dermatosis accociate with lymphomatous angioimmunoblastic lymphadenopathy*. Acta Derm Venereol 1989; 69; 445-448.
(11) Simon R, et al. *Persistent acantholytic dermatosis: A variant of transient acantholytic dermatosis (Grover's disease).* Arch Dermatol
(12) Kanitakis J, et al. *Transient acantholytic dermatosis (Grover's disease) in a renal transplant patient.* J Derm l33; 3; March 2006; 178-181.

Association with Immune Suppression

- GGD has been documented in a liver transplant case (clinically an atypical Grover-like variant)
  - Skin lesions involved the trunk
  - Skin flexural areas unaffected



Rongioletti F, et el. *Atypical variant of Galli-Galli Disease (Grover-like eruption with lentiginous freckling) in a liver transplant patient*. Am J Dermatopathol 2011: 33: 504-507

Implications

- *Systemic immune suppression may in some way trigger or effect disease penetrance in a genetically predisposed individual.*

An "E – Ticket"

(Case Presentation)

"E – Ticket"

- TL: a 37 yo caucasian female

- POH
  - Hyperopia
  - SCL wear (20/20 OU)
- PMH
  - Negative except for gall bladder surgery
  - Allergies: Sulfa and Keflex
  - FH: negative for dermatologic disorders

Tammy

- September 2002 “jacuzzi splashed” at pool party while wearing SCL’s
- One day later noted pain, redness and photophobia OD
- Treated by local MD with Q-1 hr topical antibiotics/ antivirals/steroids
- Experienced increasingly *severe* pain, photophobia and vision loss
- Referred to myself ~6 weeks after symptom onset

Tammy

- Based on history and presentation, dx'ed with *acanthamoeba keratitis*
- On initial visit:
  - Epithelial debridement culture performed (AK+)
  - PHMB + broline initiated / AB's continued / steroid weaning attempted
- Responded poorly:
  - Developed PED
  - Was steroid weaning intolerant
  - Developed progressive stromal opacification and VA loss
  - Persistent spores identified by serial confocal microscopy (Dr Irvine/Dr Hopp)
  - Eventually required addition of systemic tx for spore eradication

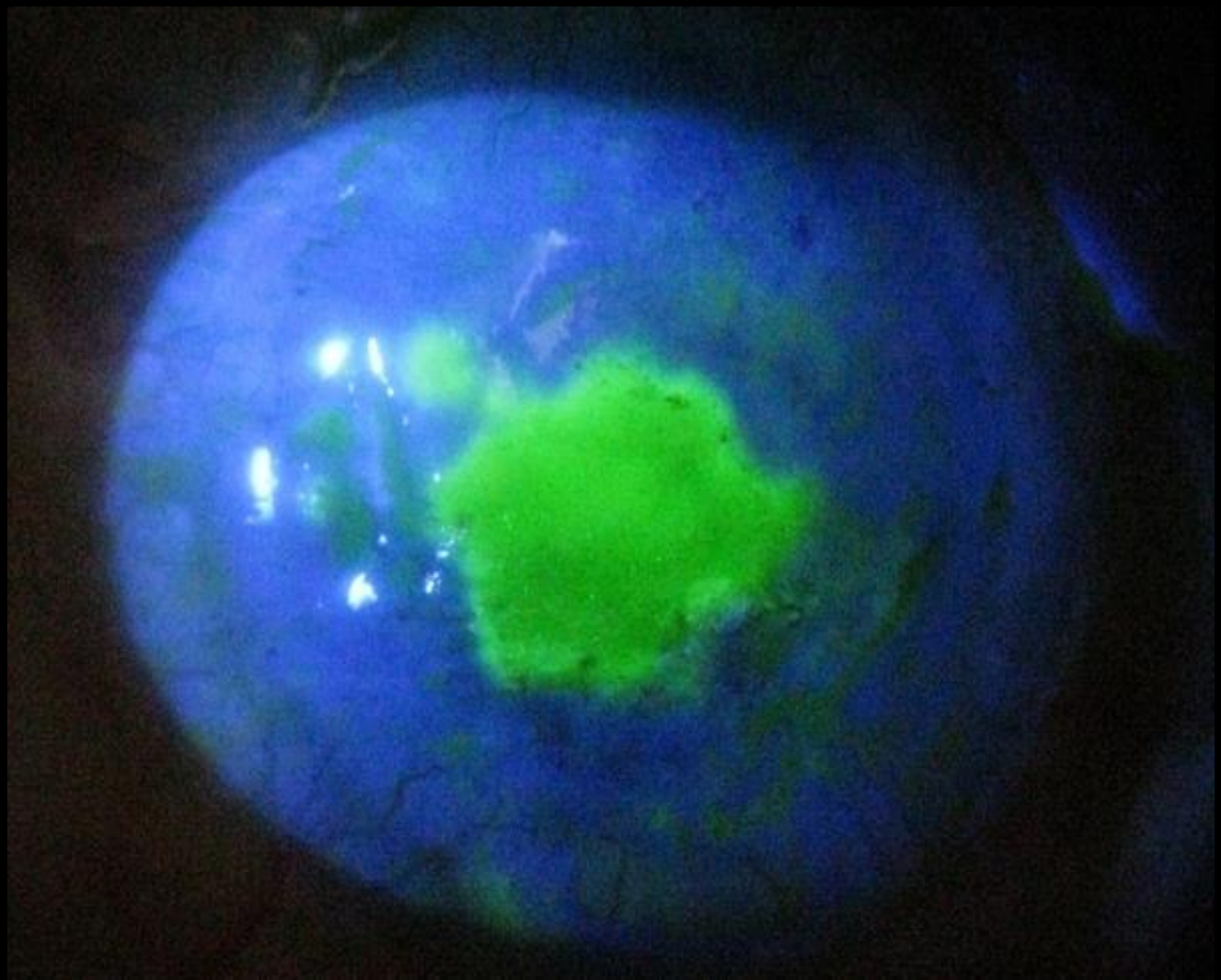
Tammy

- Based on history and presentation, dx'ed with *acanthamoeba keratitis*
- On initial visit:
  - Epithelial debridement culture performed (AK+)
  - PHMB + broline initiated / AB's continued / steroid weaning attempted

- Responded poorly:
  - Developed PED
  - Was steroid weaning intolerant
  - Developed progressive stromal opacification and VA loss
  - Persistent spores identified by serial confocal microscopy (Dr Irvine/Dr Hopp)
  - Eventually required addition of systemic tx for spore eradication

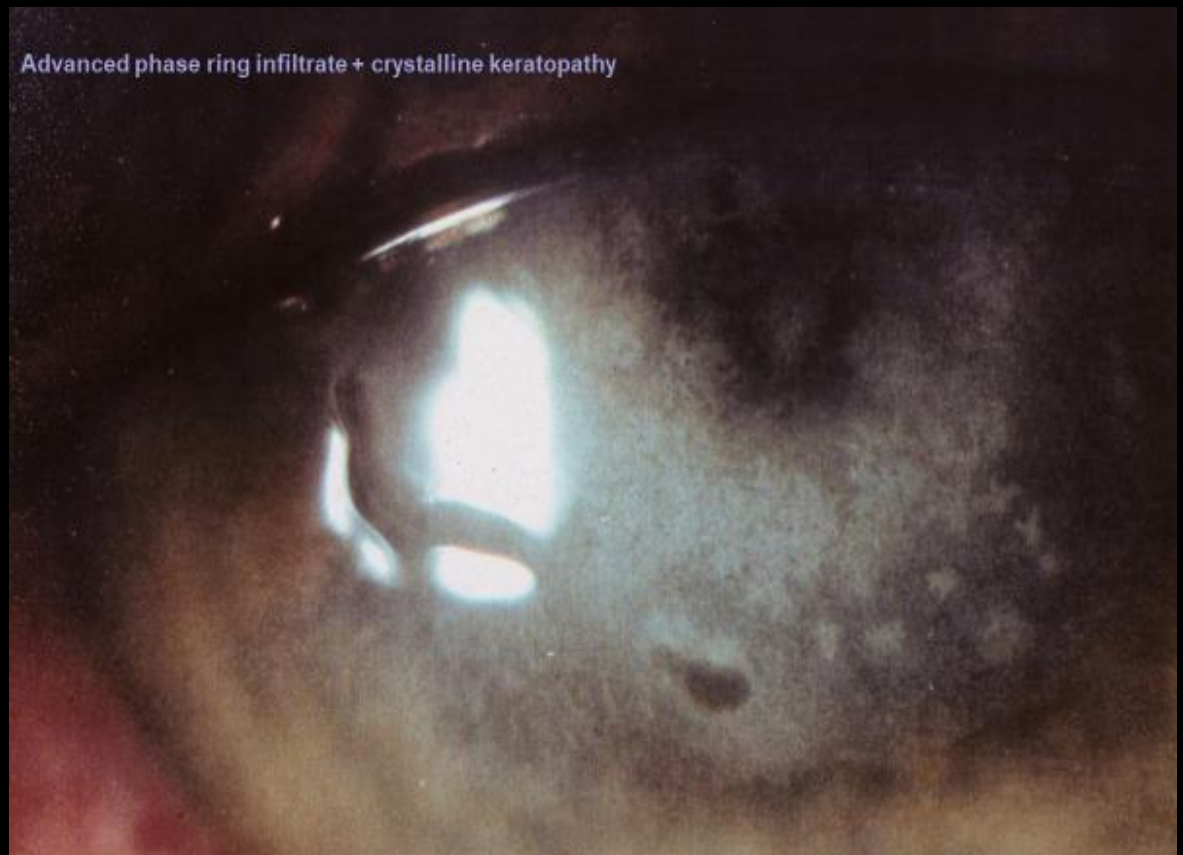
Tammy's E-Ticket Journey

- PED



Tammy's E-Ticket Journey

- PED
- Acute strep crystalline keratopathy (overlying ring infiltrate)



Tammy's E-Ticket Journey

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract

Tammy's E-Ticket Cascade

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL

Tammy's E-Ticket Journey

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma

Tammy's E-Ticket Journey

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma
- Successfully treated with vitrectomy

Tammy's E-Ticket Cascade

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma
- Successfully treated with vitrectomy
- Progressive secondary glaucoma

Tammy's E-Ticket Journey

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma
- Successfully treated with vitrectomy
- Progressive secondary glaucoma
- Placement Ahmed valve (9/08/06)

Tammy's E-Ticket Journey

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma
- Successfully treated with vitrectomy
- Progressive secondary glaucoma
- Placement Ahmed valve (9/08/06)

- Explantation of valve secondary to painful irritation and poor IOP control

Tammy's E-Ticket Cascade

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma
- Successfully treated with vitrectomy
- Progressive secondary glaucoma
- Placement Ahmed valve (9/08/06)
- Explantation of valve secondary to painful irritation and poor IOP control

- Repeat shunt (Doheny; Dr Brian Francis)

Tammy's E-Ticket Journey

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma
- Successfully treated with vitrectomy
- Progressive secondary glaucoma
- Placement Ahmed valve (9/08/06)
- Explantation of valve secondary to painful irritation and poor IOP control
- Repeat shunt (Doheny; Dr Brian Francis)

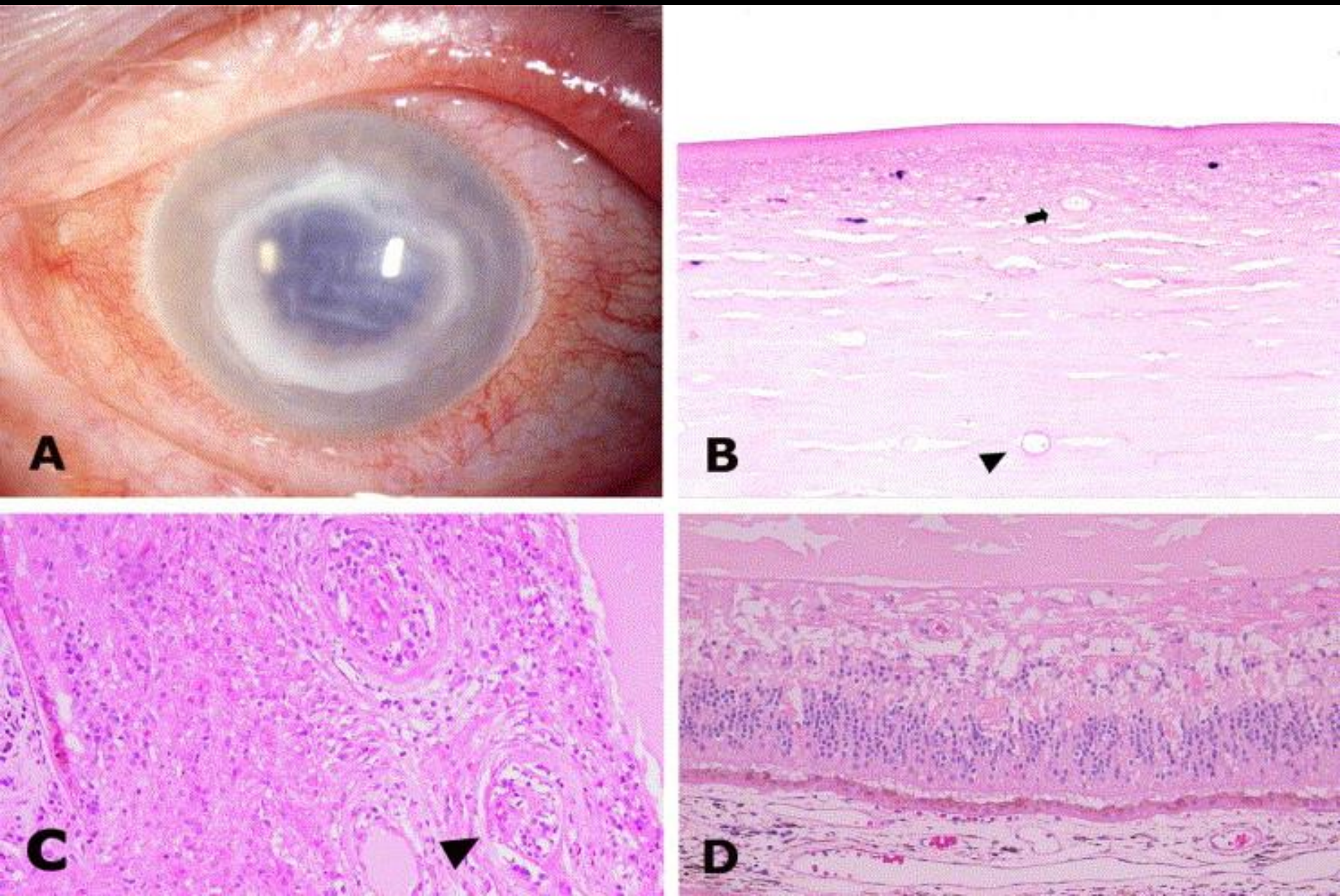
- Penetrating keratoplasty with AMT

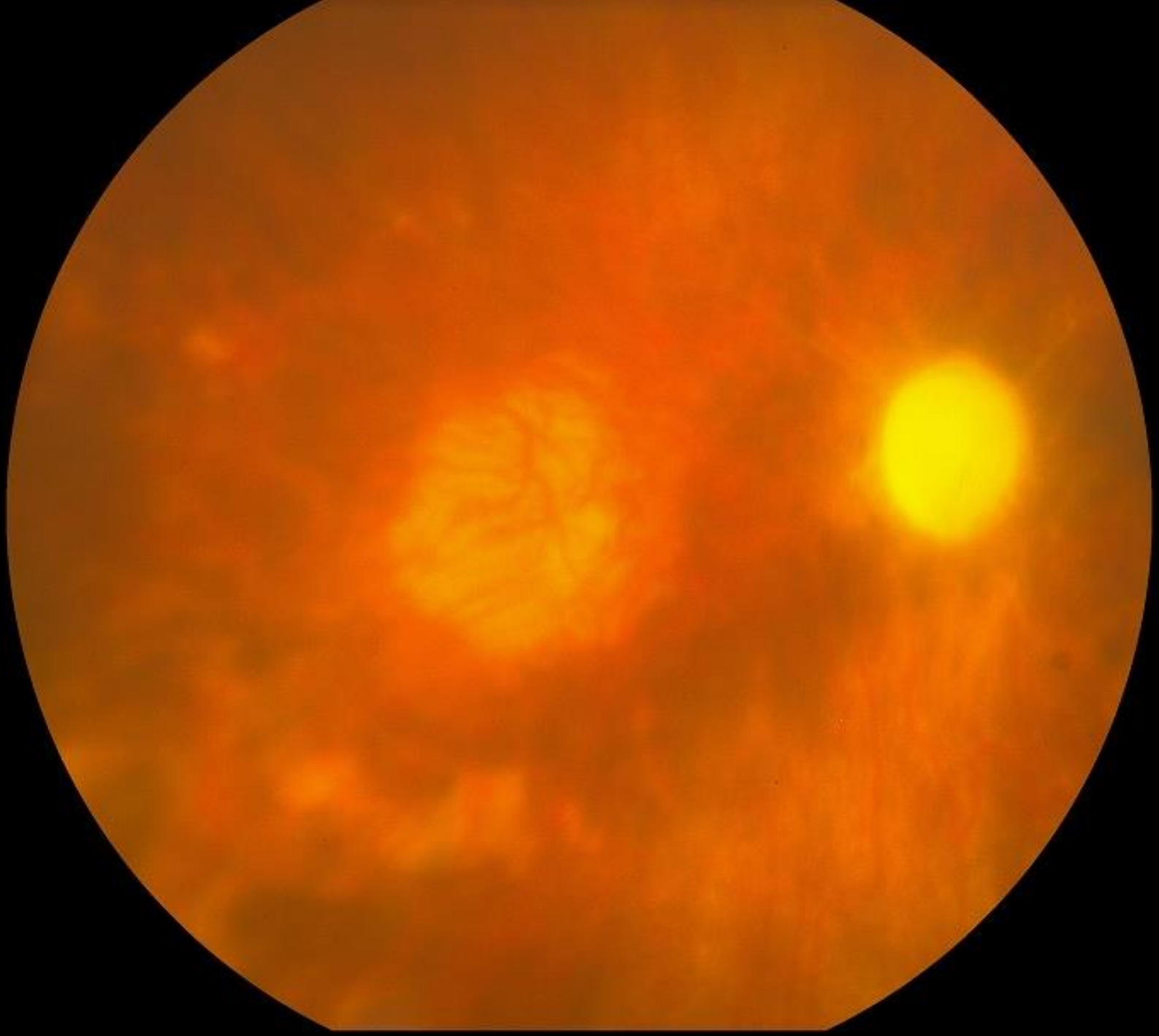
Tammy's E-Ticket Journey

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma
- Successfully treated with vitrectomy
- Progressive secondary glaucoma
- Placement Ahmed valve (9/08/06)
- Explantation of valve secondary to painful irritation and poor IOP control
- Repeat shunt (Doheny; Dr Brian Francis)
- Penetrating keratoplasty with AMT

- *Posterior Ischemic Syndrome*

Posterior Ischemic Syndrome





Tammy's E-Ticket Journey

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma
- Successfully treated with vitrectomy
- Progressive secondary glaucoma
- Placement Ahmed valve (9/08/06)
- Explantation of valve secondary to painful irritation and poor IOP control
- Repeat shunt (Doheny; Dr Brian Francis)
- Penetrating keratoplasty with AMT
- *Posterior Ischemic Syndrome*

- Retrobulbar alcohol injection (unsuccessful)

Tammy's E-Ticket Journey

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma
- Successfully treated with vitrectomy
- Progressive secondary glaucoma
- Placement Ahmed valve (9/08/06)
- Explantation of valve secondary to painful irritation and poor IOP control
- Repeat shunt (Doheny; Dr Brian Francis)
- Penetrating keratoplasty with AMT
- *Posterior Ischemic Syndrome*
- Retrobulbar alcohol injection (unsuccessful)

- Progressive anterior dislocation of PC IOL (to corneal touch)

Tammy's E-Ticket Journey

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma
- Successfully treated with vitrectomy
- Progressive secondary glaucoma
- Placement Ahmed valve (9/08/06)
- Explantation of valve secondary to painful irritation and poor IOP control
- Repeat shunt (Doheny; Dr Brian Francis)
- Penetrating keratoplasty with AMT
- *Posterior Ischemic Syndrome*
- Retrobulbar alcohol injection (unsuccessful)
- Progressive anterior dislocation of PC IOL to corneal touch

- 2009 developed chronic pruritic rash (Grover disease distribution)

Tammy's E-Ticket Journey

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma
- Successfully treated with vitrectomy
- Progressive secondary glaucoma
- Placement Ahmed valve (9/08/06)
- Explantation of valve secondary to painful irritation and poor IOP control
- Repeat shunt (Doheny; Dr Brian Francis)
- Penetrating keratoplasty with AMT
- *Posterior Ischemic Syndrome*
- Retrobulbar alcohol injection (unsuccessful)
- Progressive anterior dislocation of PC IOL to corneal touch
- Developed chronic pruritic Grover distribution rash (2009)

- Second tube shunt explantation with concomitant CPC (10/09)

Tammy's E-Ticket Cascade

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma
- Successfully treated with vitrectomy
- Progressive secondary glaucoma
- Placement Ahmed valve (9/08/06)
- Explantation of valve secondary to painful irritation and poor IOP control
- Repeat shunt (Doheny; Dr Brian Francis)
- Penetrating keratoplasty with AMT
- *Posterior Ischemic Syndrome*
- Retrobulbar alcohol injection (unsuccessful)
- Progressive anterior dislocation of PC IOL to corneal touch
- Developed chronic pruritic Grover distribution rash (2009)
- Second tube shunt explantation with concomitant CPC (10/09)
- Repeat penetrating keratoplasty with IOL explantation

- Total retinal detachment (3/29/13)

Tammy's E-Ticket Journey

- PED
- Acute strep crystalline keratopathy
- Acute onset white mature cataract
- Successful CE + PC IOL
- Acute onset of malignant glaucoma
- Successfully treated with vitrectomy
- Progressive secondary glaucoma
- Placement Ahmed valve (9/08/06)
- Explantation of valve secondary to painful irritation and poor IOP control
- Repeat shunt (Doheny; Dr Brian Francis)
- Penetrating keratoplasty with AMT
- *Posterior Ischemic Syndrome*
- Retrobulbar alcohol injection (unsuccessful)
- Progressive anterior dislocation of PC IOL to corneal touch
- Developed chronic pruritic Grover distribution rash (2009)
- Second tube shunt explantation with concomitant CPC (10/09)
- Repeat penetrating keratoplasty with IOL explantation
- Total retinal detachment

- Galli-Galli disease diagnosed (10/12/14)

Tammy's Galli-Galli Disease

- Initially diagnosed as "gluten" allergy
- Ultimately required 5 years/5 dermatologist for correct diagnosis
- Definitive dx made by Dermatopathology Service at UCSF
- Underwent ~successful UV-B phototherapy

Tammy's E-Ticket Journey

- Eviseration 9/15/15

Tammy's E-Ticket Journey

- Eviseration 9/15/15
- Galli-Galli disease continues

Tammy's E-Ticket Journey

- Eviseration 9/15/15
- Galli-Galli disease continues
- Received 13 years worth of continuous and at times high dose topical steroids

Summary

- TL represents only the ~28th case of GGD ever reported

Summary

- TL represents only the ~28th case of GGD ever reported
- Clinically manifested as Grover-like variant of GGD

Summary

- TL represents only the ~28th case of GGD ever reported
- Clinically manifested as Grover-like variant of GGD
- Grovers Disease has strong/well documented association with immune suppression including organ transplantation

Summary

- TL represents only the ~28th case of GGD ever reported
- Clinically manifested as Grover-like variant of GGD
- Grovers Disease has strong/well documented association with immune suppression including organ transplantation
- Documented case of Grover-like variant GGD associated with organ transplant immune suppression

Summary

- TL represents only the second organ transplant (PK) associated case of GGD ever reported

Summary

- TL may represent the first ever report of a *corneal transplant associated noninfectious systemic disease (GGD)*

Summary

- TL may also represent the first ever report of a *topical steroid immune suppression associated noninfectious systemic disease (GGD)*

Thank You