Clinicopathologic Correlation: Challenging Cases from Stanford

Kerri E. Rieger, MD, PhD
Departments of Pathology and Dermatology
Stanford University School of Medicine

No relevant disclosures

Case 1

- 40 year old female presents with several week history of highly pruritic, diffuse facial rash
- PMH: SLE complicated by antiphospholipid antibody syndrome, chronic kidney disease, acute cutaneous lupus, discoid lupus on the face and scalp
- Medications: prednisone, mycophenolate mofetil, hydroxychloroquine, methotrexate

Viral-associated trichodysplasia spinulosa (VATS)

- Rare disease first described by Haycox et al in 1999 (J Investig Dermatol Symp Proc)
- AKA pilomatrix dysplasia, trichodysplasia of immunosuppression, cyclosporine-induced folliculodystrophy
- Occurs in immunosuppressed patients
- Affects children and adults with no known sex predilection

VATS: clinical findings

- Asymptomatic to pruritic folliculocentric papules with keratotic spicules
- Central face and ears; occasionally trunk and extremities
- Variable nonscarring alopecia, mostly affecting the eyelashes and eyebrows
- Can progress to an infiltrated appearance or leonine facies
**VATS: clinical findings**

- Asymptomatic to pruritic folliculocentric papules with keratotic spicules
- Central face and ears; occasionally trunk and extremities
- Variable nonscarring alopecia, mostly affecting the eyelashes and eyebrows
- Can progress to an infiltrated appearance or leonine facies

**VATS: clinical differential diagnosis**

- Folliculitis
- Keratosis pilaris
- Facial spiky follicular hyperkeratosis associated with multiple myeloma
- Follicular mucinosis
- Trichostasis spinulosa
- Acne comedones
- Lichen spinulosus
- Lichen nitidus

**VATS: histopathology**

- Dilated, dysmorphic hair follicles

**VATS: histopathology**

- Dilated, dysmorphic hair follicles
- Absent or small hair papilla
- Very thin rim of germinative cells
- Massive proliferation of cells containing trichohyaline granules

**VATS: etiology**

- New human polyomavirus named trichodysplasia-associated polyomavirus (TSPyV) isolated in 2010
- 70% of adults exhibit seroconversion, with about one-third showing seroconversion by early childhood.
- Primary infection with TSPyV causes VATS in immunocompromised patients; sometimes coincides with cerebral lesions and neuroendocrine symptoms
**VATS: pathogenesis**

- Mostly unknown
- TSPyV disrupts the retinoblastoma pathway, a probable cause of inner root sheath cell hyperproliferation

**VATS: management**

- Reduction of immunosuppression
- Topical antivirals (acyclovir, cidofovir)
- Oral valganciclovir
- Topical imiquimod

**Viral-associated trichodysplasia spinulosa: summary**

- Rare disease of immunocompromised patients caused by a polyomavirus
- Characterized by folliculocentric papules with spicules on the central face
- Histopathology: distorted follicles with abundant, enlarged trichohyaline granules

**Case 2**

- 57 year-old female with 10 year history of indurated, disfiguring plaques and nodules on the face
Silicone

• “Silicone” describes a large family of synthetic polymers containing elemental silicon
• Widely used filler for soft tissue augmentation
• Oil, gel, or solid rubber (elastomers) forms
• Irreversible
• Generally well tolerated, but adverse effects can be dramatic and irreversible

Silicone: some history

• 1948: publication on toxicology - ‘physiologically inert’
• Early 1950s: doctors in Japan and Las Vegas began injecting it to enlarge women’s breasts
  – Complications, including death
• Mid 1950’s: Orentreich pioneered the use of tiny amounts of silicone to fill facial wrinkles
• 1992: FDA banned liquid silicone in the face
• 1997: FDA approved liquid silicone for medical use - to correct detached retinas

Singer, New York Times, Jan 26 2006
Nairns, Plastic and Reconstructive Surgery 2006

Silicone: adverse effects

• Localized small nodules of silicone without an inflammatory response
• Exuberant foreign body reaction with induration, erythema, swelling
• Silicone migration to distant sites, with accompanying foreign body reaction

Silicone: adverse effects

• Localized small nodules of silicone with sparse inflammation
• Exuberant localized foreign body reaction with induration, erythema, swelling
• Silicone migration to distant sites, with accompanying foreign body reaction

Silicone: histopathology

Silicone liquid reaction (‘siliconoma’)

Exuberant foreign body reaction (‘silicone granuloma’)

Requena et al, JAD 2010
True or false?

- Silicone is birefringent under polarized light.

**False.** Angulated translucent birefringent particles occasionally seen in silicone granulomas probably result from impurities in non-medical grade silicone injected by nonprofessionals, or from deposition of talc introduced at the time of the injection or surgery.

**Case 2: more history**

- 57 year-old female with 10 year history of indurated, disfiguring plaques and nodules on the face
- Several year history of painful nodules on extremities and trunk with systemic symptoms

**Further workup**

- CT scans of the orbit and chest suggested possible granulomas in the lungs and orbits. No evidence of leakage from breast implants.
- MRI showed axillary and mediastinal lymphadenopathy
- Negative quantiferon and histoplasma antibodies
- The glabellar and arm masses were surgically excised.

**Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) syndrome**

- First described in 2011 by Shoenfeld
- Spectrum of immune-mediated diseases triggered by an adjuvant stimulus such as chronic exposure to silicone, aluminum and other adjuvants
- Characterized by a combination of symptoms that do not fulfill any diagnostic criteria for a well-defined auto-immune connective disease
Systemic reported complaints/diseases related to injectable fillers
Alijotas-Reig, Semin Arthritis Rheum 2013

Management of inflammatory late-onset adverse effects related to implant fillers management
Alijotas-Reig, Semin Arthritis Rheum 2013

Silicone granulomas: summary
- Silicone is one of the most controversial substances in cosmetic medicine
- Histopathology of silicone granulomas: foreign body reaction with ‘swiss cheese’ appearance
- ‘ASIA’ syndrome is a controversial entity; at least some cases caused by silicone

Case 3
Excision of melanoma in situ from the left posterior calf of a 69 year old female.
Reexcision PNI

• First described in reexcision specimens of two melanocytic lesions (Stern and Haupt, AJSP, 1990)
• Histopathology:
  – Mature squamous epithelium in perineural space of cutaneous nerves in reexcision specimens
  – Squamous epithelium may form complete cuff around nerve fascicle
• Pathogenesis: ? reactive/reparative process, probably from regenerating traumatized eccrine ducts

Stern and Haupt, AJSP, 1990

Reexcision PNI

• Later noted in reexcision specimens of other cutaneous neoplasms, including BCC and SCC
• Distinguishing it from carcinomatous PNI?
  Guidelines favoring reexcision PNI:
  – absence of perineural spread beyond the previous biopsy site
  – benign appearance of the perineural epithelial cells in contrast to the appearance of the original tumor
  – absence of residual epithelial tumor in the vicinity of the involved perineurium, and eccrine ducts adjacent to the involved nerves

Dunn et al, JCP 2008

Perineural invasion

• In the presence of a malignancy, diagnosed as cytologically malignant cells in the perineural space of nerves
• ~6% of cutaneous SCC, ~3% of BCC, and 80% of microcystic adnexal carcinoma
• Indicates higher risks of tumor metastasis, recurrence, and poor clinical outcome
  – 64% 5-year disease-specific survival for patients with SCC with PNI versus 91% for SCC without PNI (Clayman et al, JCO 2005)

Dunn et al, JCP 2008
• Biopsy from the back of a 62 year old female
• No known prior procedure or trauma at the site

The best diagnosis is:

A. Eccrine carcinoma
B. Perineural invasion of SCC
C. Reexcision perineural invasion
D. Peritumoral fibrosis
E. Epithelial sheath neuroma

Epithelial Sheath Neuroma (ESN)

• First described by Requena et al (AJSP 2000)
• Histopathology
  – Enlarged nerve fibers ensheathed by squamous epithelium with variable keratinization, located in the superficial dermis
  – Surrounding dermis showed delicate fibroplasia with mucin and mild inflammatory cell infiltrate of lymphocytes and few plasma cells
  – No associated in situ or invasive carcinoma and no changes of previous surgery

Clinical
– Benign, acquired lesion, usually on back of middle-aged or elderly women
– No prior procedure/trauma at the site
– Clinically misdiagnosed as BCC or inflamed nevus
– No lesions have recurred after biopsy
**Epithelial Sheath Neuroma (ESN)**

- How to distinguish ESN from carcinomatous PNI?
  - Cytopathology may be indistinguishable
  - Architecture shows increased number and size of nerve trunks high in the reticular dermis

**Peritumoral fibrosis**

- Concentric rings of fibrous tissue with nests of tumor cells → may mimic microscopic PNI

**Peritumoral fibrosis**

- Seen in 5% of SCCs and 6% of BCCs
- Concurrent real PNI is often seen, so it’s a more sensitive marker of true PNI than perineural inflammation
  - Incidence of PNI in BCC with peritumoral fibrosis was 29%
  - Incidence of PNI in SCC with peritumoral fibrosis was 50%

**Reparative perineural hyperplasia**

- Prominent proliferation of perineurium of regenerating nerves in healing surgical wounds
- Concentric rings of bland spindle-shaped cells envelop a nerve adjacent to scarring and reparation from prior surgery
- Distinguishing from SCC:
  - Lack of cellular stippling, organized concentric pattern of growth, and lack of mitotic activity
  - Negative for S100 and cytokeratins
  - Positive for EMA (as would be seen in normal perineural cells)

**Excision of a recurrent basal cell carcinoma in a 62 year old man**

![Excision image](image-url)

**Dunn et al., JCP 2008**

**Peritumoral fibrosis**

- Peritumoral fibrosis in BCC and SCC
- Real nerve fiber
- Permanent sections
- Hassanein et al., Derm Surg 2005

**Peritumoral fibrosis**

- Concentric rings of fibrous tissue with nests of tumor cells → may mimic microscopic PNI
- Nerve fibers contain smaller, plump neuroid cells with swirling and wavy fibrils; more vacuolated
- May need IHC (sox10, s100)

**Reparative perineural hyperplasia**

- Prominent proliferation of perineurium of regenerating nerves in healing surgical wounds
- Concentric rings of bland spindle-shaped cells envelop a nerve adjacent to scarring and reparation from prior surgery
- Distinguishing from SCC:
  - Lack of cellular stippling, organized concentric pattern of growth, and lack of mitotic activity
  - Negative for S100 and cytokeratins
  - Positive for EMA (as would be seen in normal perineural cells)
Perineural invasion

- Indicates higher risks of tumor metastasis, recurrence, and poor clinical outcome
- Important to distinguish carcinomatous PNI from its mimics:
  - Reexcision perineural invasion
  - Peritumoral fibrosis
  - Epithelial sheath neuroma
  - Reparative perineural hyperplasia

Acknowledgements

Stanford Dermatopathology
Jinah Kim
Rob Novoa
Ursula Liang
Kate Roy
Daniela DeStefano

Stanford Dermatology
Marilynn Pol-Rodriguez
Tyler Hollmig
Sumaira Aasi
Matthew Lewis