AtlanticDerm CONFERENCE

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Diagnosis and Management of Rare Nonmelanoma Skin Cancers

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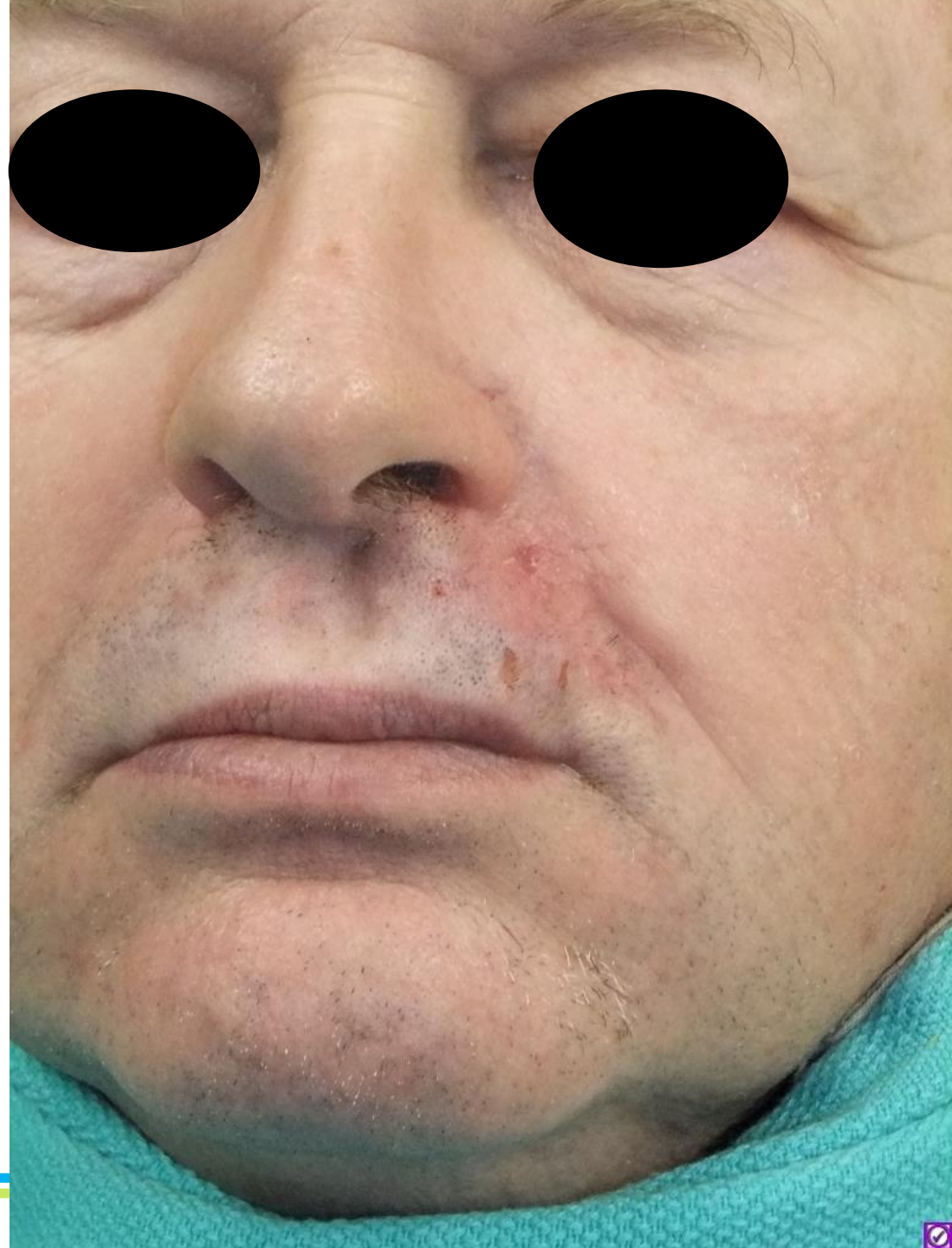
I have no relevant conflicts to disclose

Rare Non-melanoma Skin Cancers: Diagnosis, Management & Treatment

- Squamoid eccrine ductal carcinoma (SEDC)
- Microcystic adnexal carcinoma (MAC)
- Dermatofibrosarcoma protuberans (DFSP)

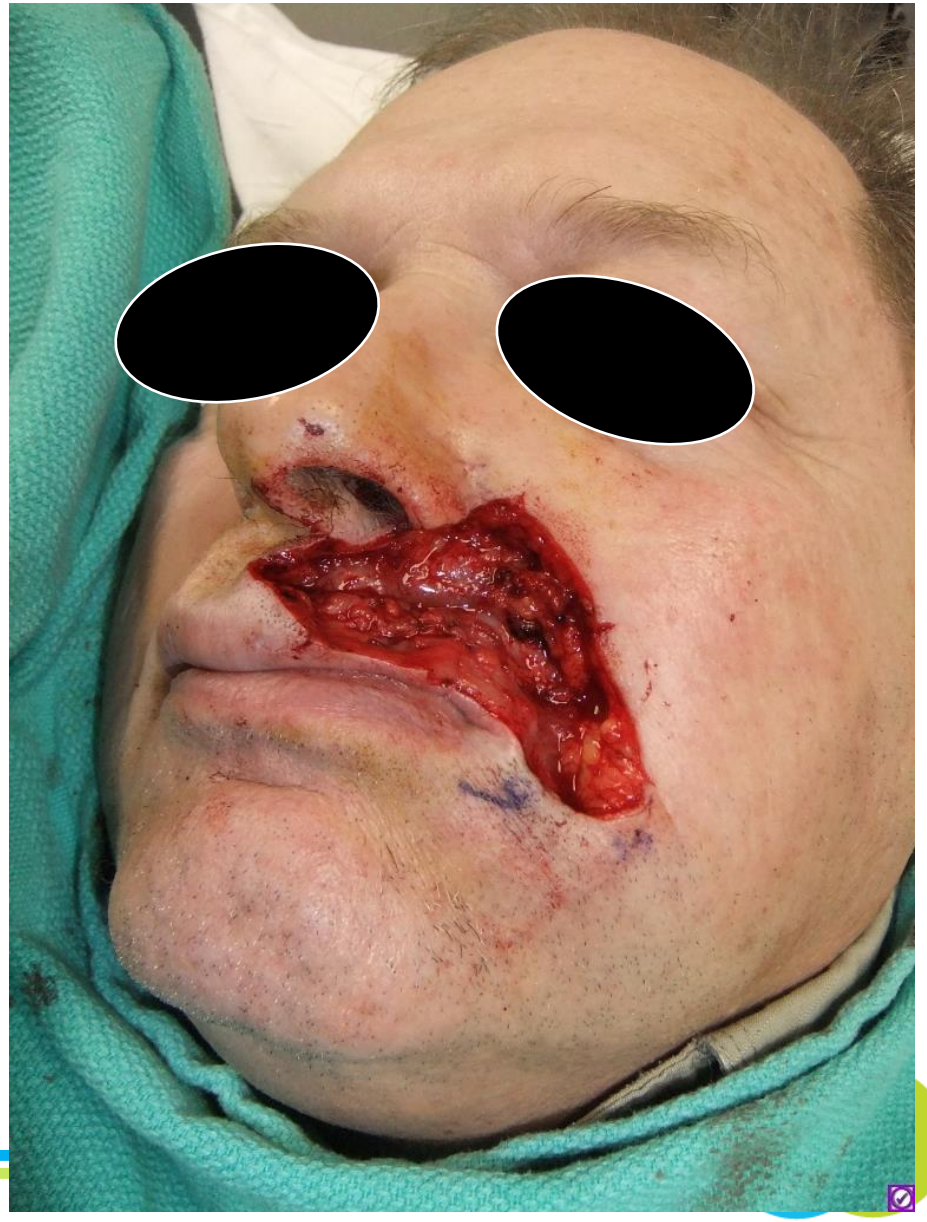
HPI

- 62 year old male truck driver presented with a 4cm pearly plaque of the left upper cutaneous lip
- Biopsy performed by ENT on 11/4/2019: consistent with morpheaform BCC
- Referred for Mohs surgery



HPI

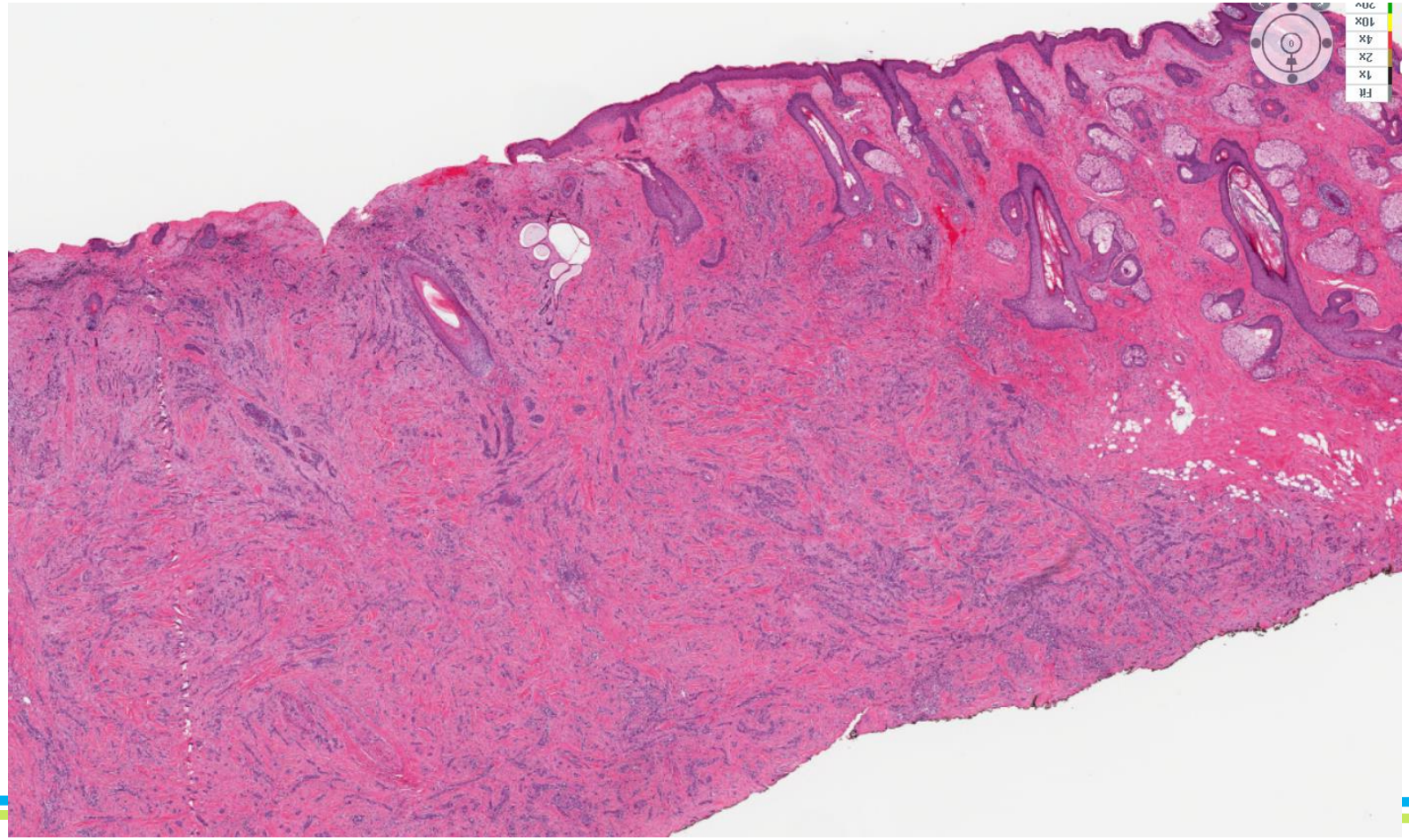
- Mohs surgery performed on 12/2/19
  - Required 3 stages to clear, with a resultant full thickness defect
  - PNI and squamous differentiation noted on Mohs sections
- Non-marginal tissue sent for permanent sections to confirm diagnosis

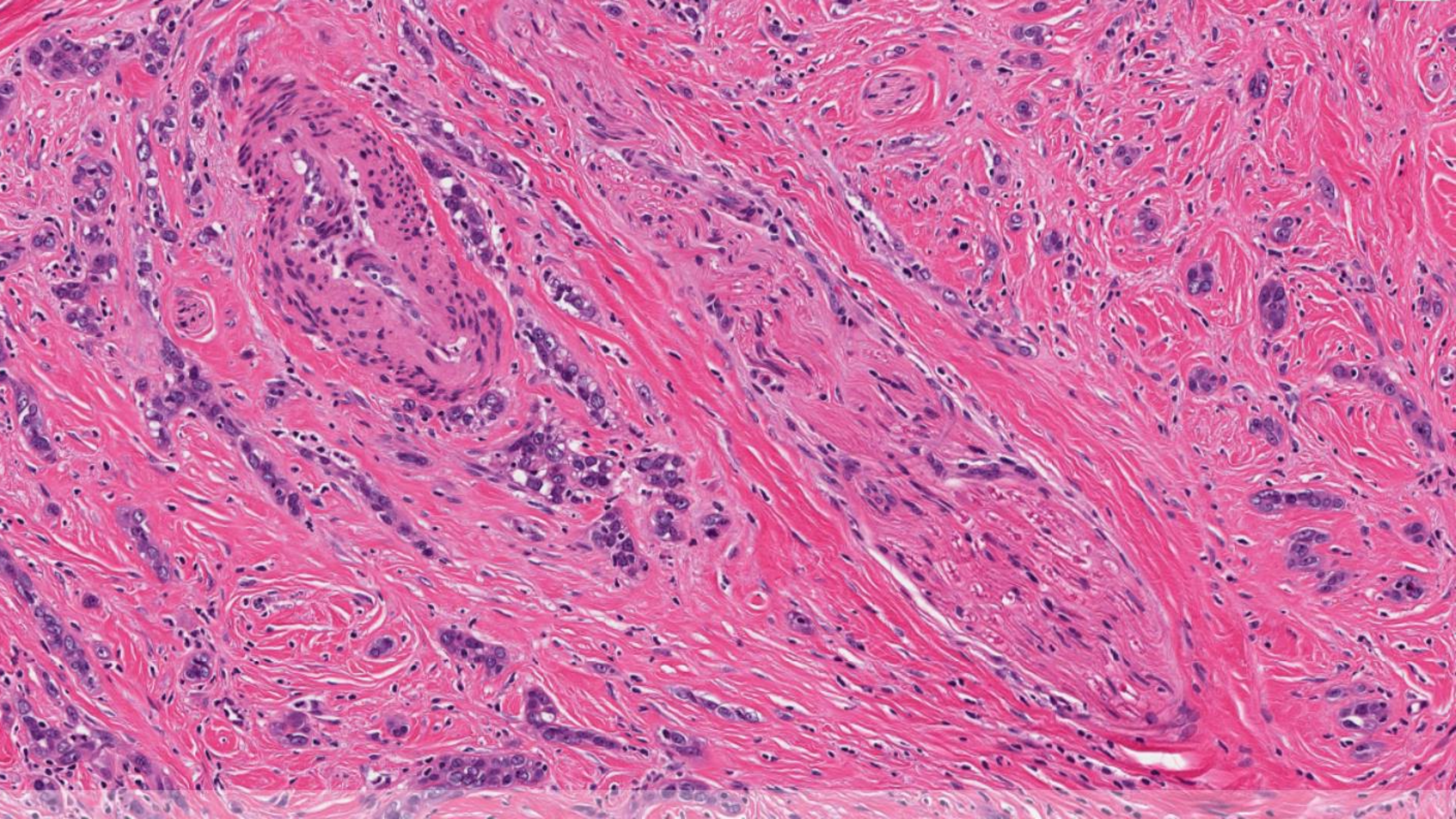


12-2-19

Pathology

- Nonmarginal tissue consistent with **squamoid eccrine ductal carcinoma**
- PNI of 0.1mm
- Positive S100, EMA, CEA and cytokeratin





HPI

- Interdisciplinary NMSC Tumor Board:
  - Recommended Radiation Oncology consult – however, patient declined XRT

- Repeat imaging and FBSE 3-12-21, 6-13-22 and 2-19-24 have been unremarkable for evidence of recurrence

Eccrine Carcinomas

- Adnexal carcinomas arising from the eccrine apparatus represent **less than 0.01%** of all cutaneous tumors
- **Ductal eccrine carcinoma** is the most common
- Nodule or plaque on the scalp, trunk or extremities of middle aged to elderly individuals
- **Up to 50%** of all eccrine carcinomas **metastasize** compared to only 0.5% of cSCC
- Clinical course is aggressive characterized by **multiple recurrences, perineural invasion, and spread to LNs and distant organs**
- Distinct histologic variants of ductal eccrine carcinoma exist, including squamoid eccrine ductal carcinoma (SEDC) with squamous metaplasia

Squamoid Eccrine Ductal Carcinoma (SEDC)

TABLE 1. Subtypes of Malignant Eccrine Tumors

Eccrine (Syringoid) Carcinoma
SEDC*
Microcystic adnexal carcinoma*
Eccrine porocarcinoma*
Eccrine hidradenocarcinoma
Polymorphous sweat gland carcinoma

*Tumors reported to have squamoid differentiation.

Am J Dermatopathol Volume 44, Number 4, April 2022

Squamoid Eccrine Ductal Carcinoma

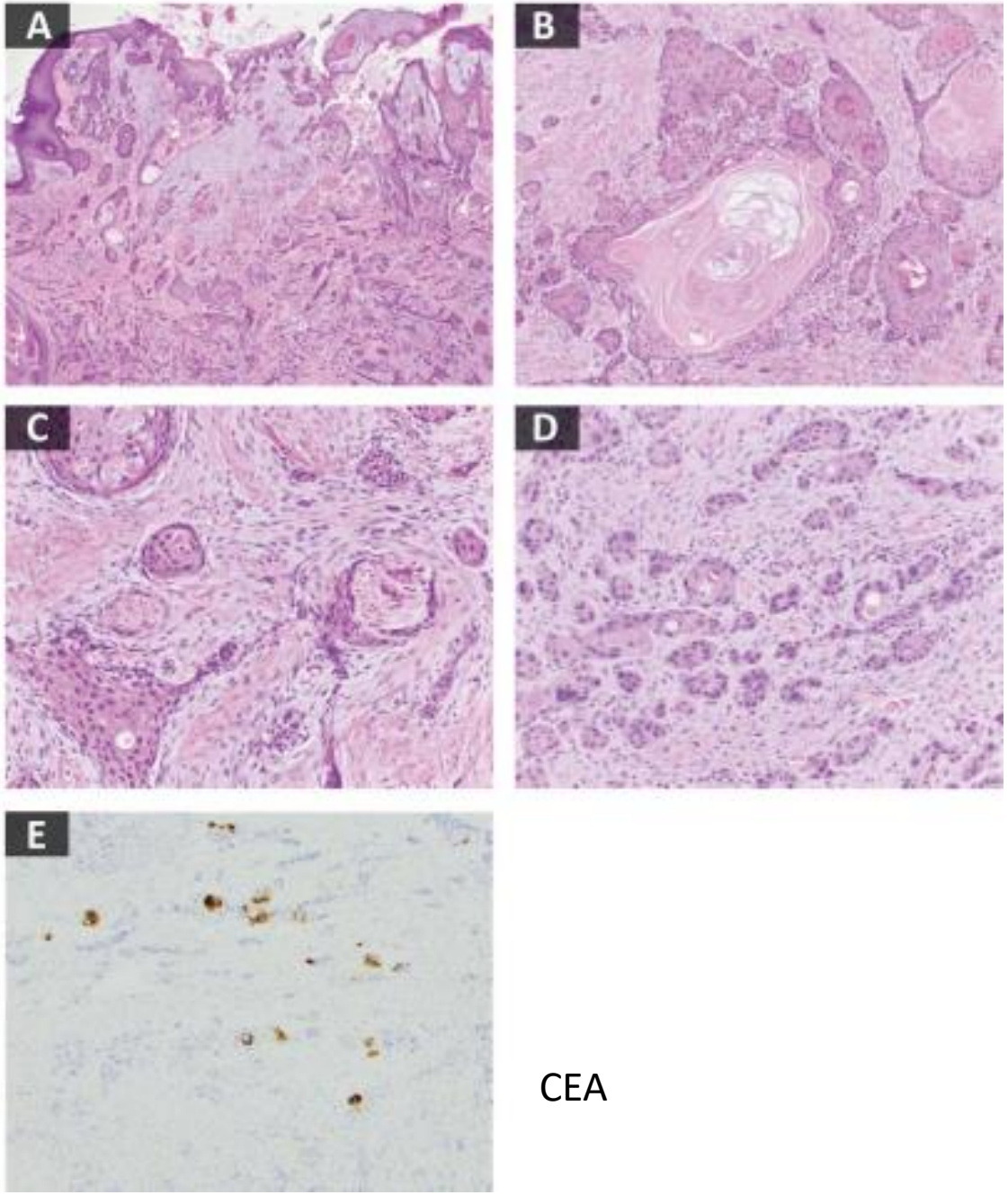
- Exceedingly rare, first 3 cases reported in 1997
  - Wong et al Histopathology 1997; 30: 288–293
- Almost **half** of the reported cases of SEDC are initially misdiagnosed (#1 is SCC)
- Important to diagnose correctly due to tendency of SEDC to recur (25%) and metastasize (13%)
- It is unclear whether SEDC arises from eccrine ducts with subsequent squamous differentiation, represents a subtype of SCC, or is truly a hybrid tumor

SEDC Histology

- Characteristic biphasic growth pattern: superficial squamous differentiation with deeper aspects composed of infiltrative cords and strands of atypical epithelial cells
  - Superficial aspect indistinguishable from SCC: may show horn cysts, squamous eddies, or intercellular bridging

- Tumors are often deeply invasive into the subcutis
- PNI (27%), LVI (6%), and tumor necrosis are often noted
- Cystic structures reminiscent of MAC have NOT been described in SEDC

- IHC can assist with diagnosis
  - EMA and CEA will highlight ductal elements
  - CEA positivity supports adnexal origin (typically negative in SCC)
  - p63 and CK5/6 supports primary cutaneous origin



CEA

Whole-Exome Sequencing of a Case of Squamoid Eccrine Ductal Carcinoma Reveal Similarities With Cutaneous Squamous Cell Carcinoma

Vanden Lamar Grube, Sarah Ahmed, Kelly McCoy, Shaymaa Ashi, and Farhaan Hafeez

Am J Dermatopathol 2023 Jul 1;45(7):495-498.

- 79 yowf with PCV on ruxolitinib with large SEDC on back
- Whole exome sequencing
- SEDC had very few genetic similarities to known mutations in other eccrine carcinomas (e.g. MAC, porocarcinoma, adenoid cystic carcinoma, hidradenocarcinoma)

Whole-Exome Sequencing of a Case of Squamoid Eccrine Ductal Carcinoma Reveal Similarities With Cutaneous Squamous Cell Carcinoma

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- Genomic aberrations noted in SEDC were similar to those reported with cSCC, including high mutational burden, UV signature mutations, and mutations in shared genes
- SEDC may start as a well differentiated cSCC that subsequently undergoes divergent differentiation focally to resemble a sweat gland malignancy
- Ducts in SEDC may arise from adnexal stem cells that undergo eccrine or apocrine differentiation

TABLE 1. Gene Mutations Detected by Whole-Exome Sequencing

Gene	Mutation
ASXL1	G642 fs*
COL2A1	G384S*
TP53	R196*†
	W53*†
ARID2	1913-1G>A*
	Q819*†
	G638E
ATRX	N2811
FAT1	Q1244*†
	D2588N
	S1955F
KMT2D	P981S
NOTCH1	P67S
NTRK3	V687A
	G291D
PTPRD	P126S
RB1	R910Q
RET	P622L
SMARCA4	G1194K
SMARCB1	R37C
	E330K

*Pathogenic or likely pathogenic variant; the absence implies variant of uncertain significance.
†Translation termination codon.
fs, frameshift.

Squamoid Eccrine Ductal Carcinoma

- Slight male predominance, 7th to 8th decade, rarely children
- Immunosuppression is a risk factor
- Head and neck (ear, cheek, neck), > extremities > trunk
- Solitary dermal nodule that may ulcerate
- May be present for months to up to 10 years
- Surgery is mainstay of treatment
  - LR 25% with 44 cases WLE, 0/6 Mohs surgery
- **No defined margins for excision, imaging workup or XRT recommendations**

Lim, Megan M., and Jillian A. Macdonald. "Squamoid Eccrine Ductal Carcinoma: Treatment and Outcomes." American Journal of Dermatopathology 44.4 (2022): 249-253.

SEDC: The Cleveland Clinic Experience

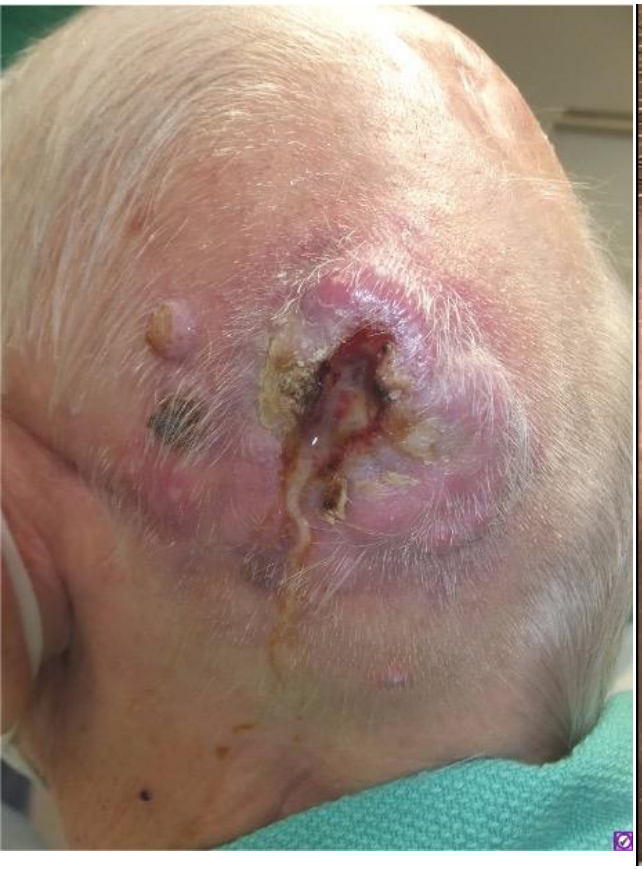
- 14 patients with SEDC, 2001-2021
- 7 males and 7 females
- Avg age at diagnosis: 71

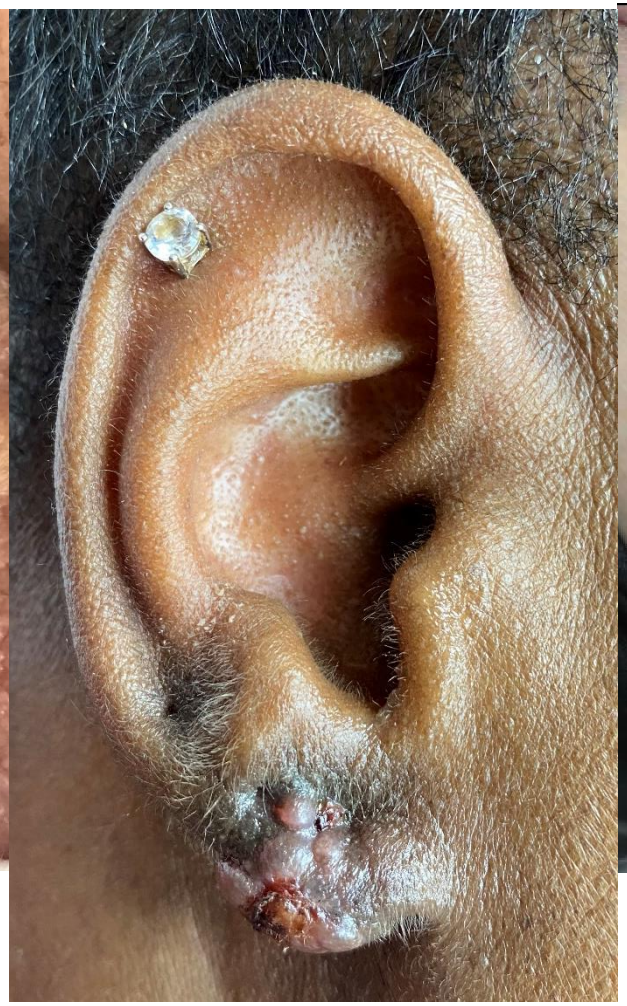
- Sites of involvement:
  - Scalp (5)
  - Back (4)
  - Upper lip (2)
  - Shoulder (1)
  - Waistline (1)
  - Finger (1)

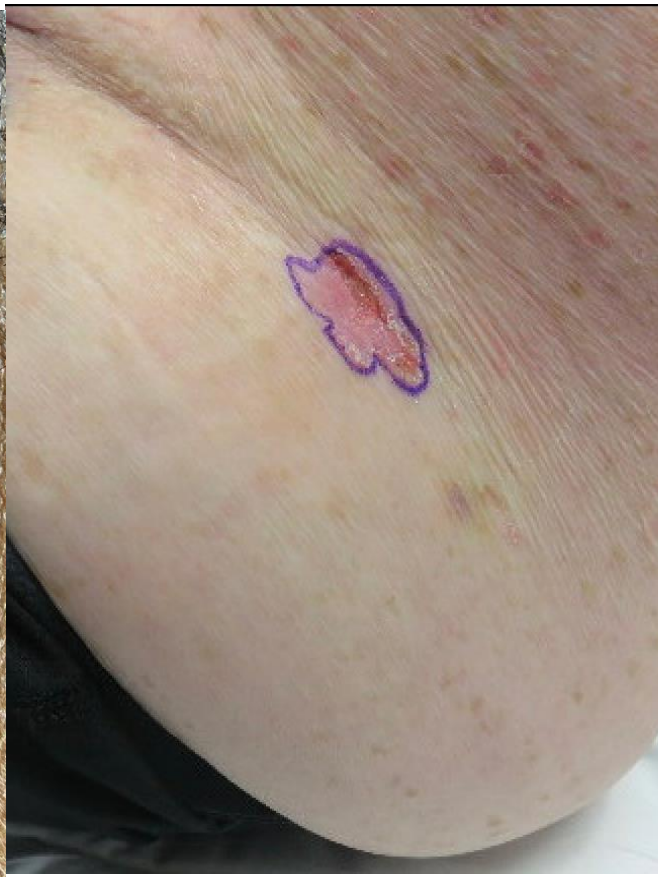
- 10/14 patients were immunosuppressed:
  - SOTR (5)
  - CLL (4)
  - Autoimmune disease with long-term corticosteroid use (1)

- 6/14 (43%) were misdiagnosed on initial biopsy (mod-poor diff SCC x 4, morpheaform BCC x 1, MAC x 1)

Clinical Appearance SEDC - CCF Series







SEDC: The Cleveland Clinic Experience

- <u>Management:</u>
  - Mohs surgery (11)
  - Staged Excision “Slow Mohs” (2)
  - Wide Local Excision (1)

- Avg Mohs stages to clear: 2.23
- PNI noted in 5/14 cases

Avg follow up time: 17 months

- 3 recurrences (2 SOTR, 1 CLL)
- Of the recurrences, 2 patients died
- One of the SOTR required amputation of his hand, later recurred again, requiring amputation of his left arm to level of upper 1/3 of humerus

- Mortality: 3/14 died of SEDC

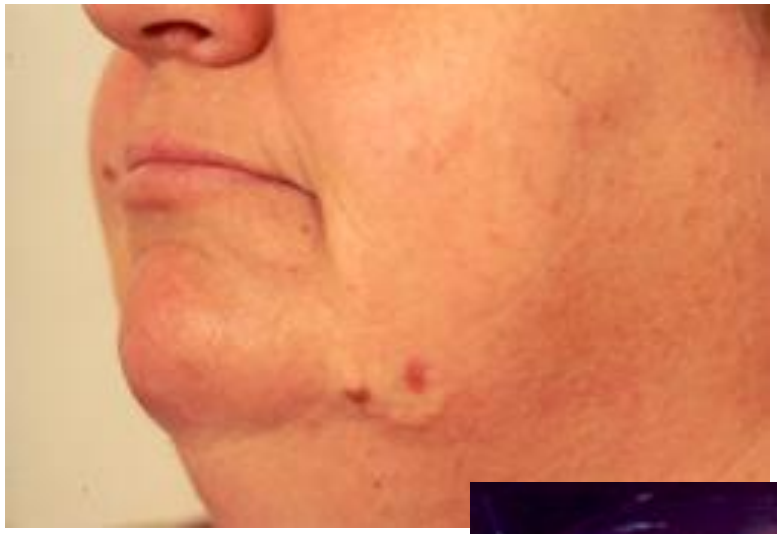
SEDC Summary

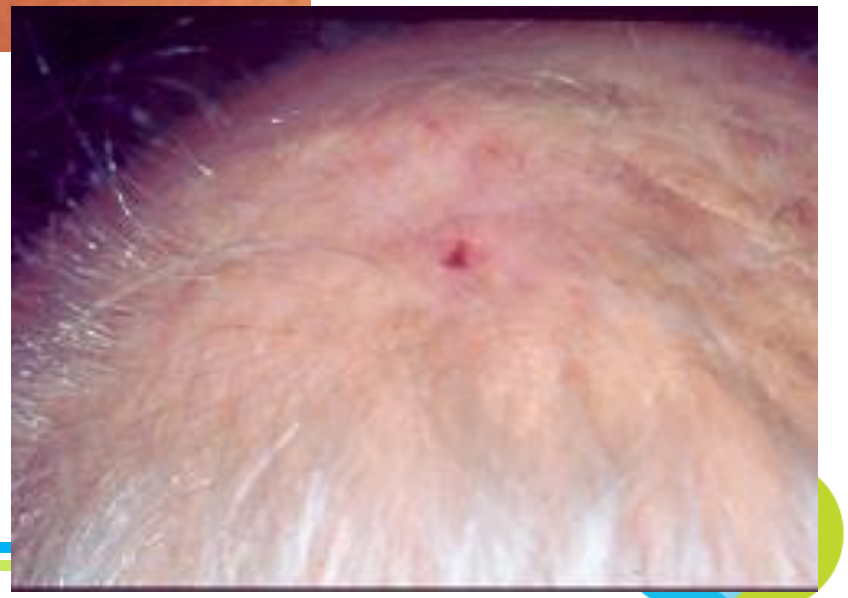
- To avoid misdiagnosis, recommend punch or excisional biopsy into fat to assess both the superficial squamous and deeper eccrine component
- If treating a presumed SCC with MMS and ductal differentiation is noted, recommend sending non-marginal tissue to evaluate for PNI and to confirm diagnosis
- Misdiagnosis, delay in diagnosis, and presence of PNI may portend poor clinical outcomes
- No standard WLE margins
- Role of XRT and systemic therapy unknown
- Close clinical and radiologic follow-up every 3-4 months x 3 years then q 6-12 months


ROCK AND ROLL HALL OF FAME AND MUSEUM

Microcystic Adnexal Carcinoma (MAC)

- Rare, malignant sweat gland tumor
- Average age 62
- Slightly more common in women
- White race >> African Americans, Asians or Pacific Islanders>Hispanics
- Most tumors occur on head and neck
- Slow growing, yellowish white plaque upper lip>cheek (mean diameter at presentation 2.8cm)
- Perineural invasion common (to date, no association with increased risk recurrence or overall survival)





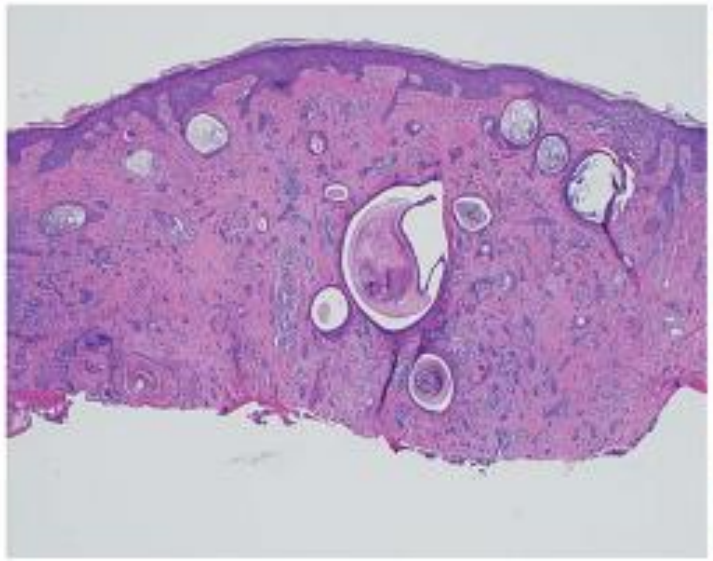
Microcystic Adnexal Carcinoma (MAC)

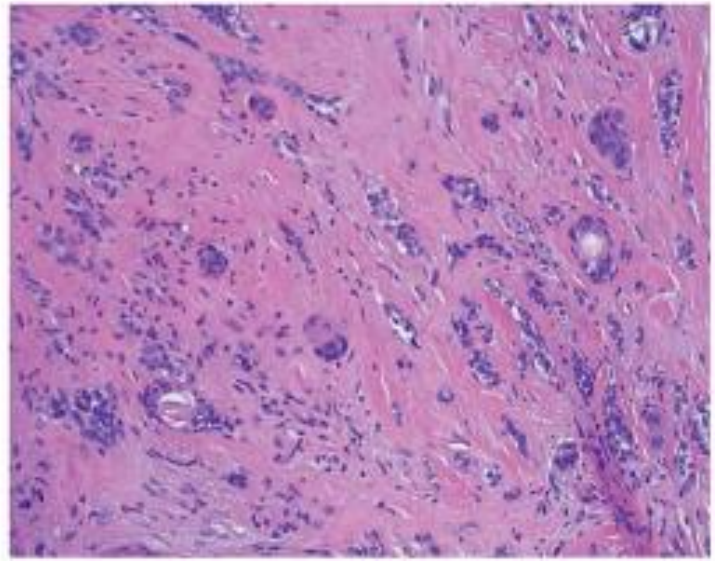
- Locally aggressive
- Extends beyond visible margins by centimeters
- Metastases rare but reported (LN 2%, distant mets 0.2%)
- MAC associated death 0.1% (2/1968 cases) – primary tumors were periocular
- 78.9% of recurrences occurred within 3 years after primary excision
- Recurrence has been reported up to 30 years later

Worley B et al. Evidence-Based Clinical Practice Guidelines for Microcystic Adnexal Carcinoma. Informed by a Systematic Review. JAMA Dermatol 2019; 155: 1059-1068.

Microcystic Adnexal Carcinoma
Histology

- Asymmetric, poorly circumscribed tumor
- Deceptively bland nests and cords of round to cuboidal basaloid cells with eosinophilic cytoplasm and small, pale staining nuclei
- Keratin-filled cysts
- Ductal structures
- Desmoplastic stroma
- Perineural invasion in up to 50%
- Cytologic atypia and mitoses rare, more prominent in deeper portions of tumor



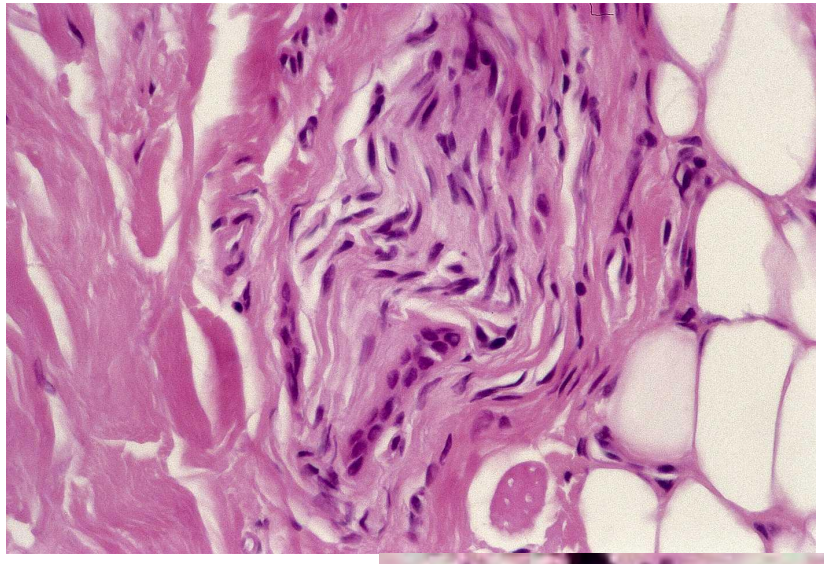


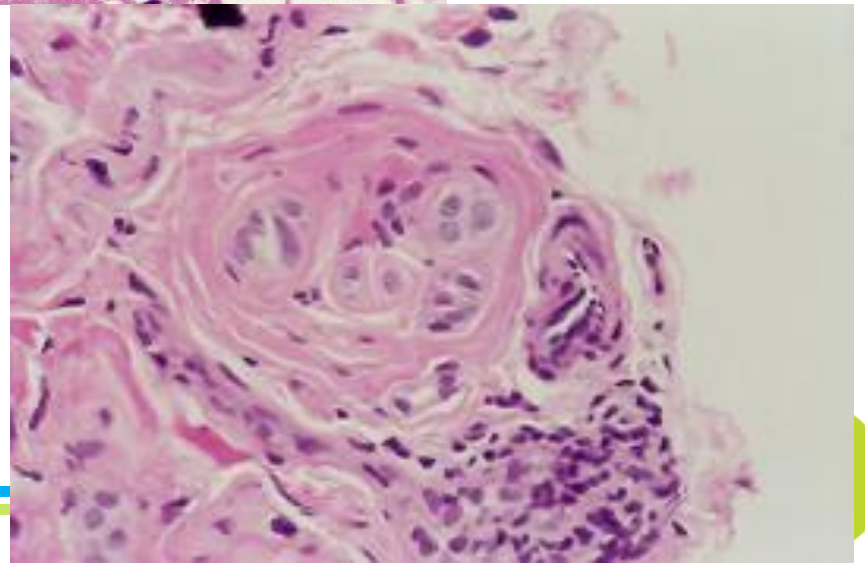
Gordon S et al. Microcystic adnexal carcinoma. Review of the Literature. Dermatol Surg 2017;43:1012–1016

Microcystic Adnexal Carcinoma

Histology

- Intramuscular, perichondrial, periosteal involvement, and permeation of vascular adventia
- “Shelving” or “skating” along fascial or capsular planes such as muscle, galea, perichondrium, periosteum
- Bony invasion
- Perineural spread intracranially





Microcystic Adnexal Carcinoma
Evaluation and Management

- Biopsies should include fat to help reach correct diagnosis
  - Superficial biopsies have led to misdiagnosis in 27%, including desmoplastic trichoepithelioma, morpheaform BCC, and syringoma
  - IHC helpful in equivocal cases: CEA, EMA, CK20, Ber-EP4
- Compete skin and LN exam, and relevant neurologic exam
- MRI to assess soft tissue extension in cosmetically and functionally crucial sites, and assess PNI
- CT with bone windows to assess bone invasion

Worley B et al. Evidence-Based Clinical Practice Guidelines for Microcystic Adnexal Carcinoma. Informed by a Systematic Review. JAMA Dermatol 2019; 155: 1059-1068.

Microcystic Adnexal Carcinoma
Evaluation and Management

- Complete excision with clear margins, while preserving function and cosmesis
  - **Mohs surgery**
    - Surgical defects after Mohs median of **4 fold larger than preop diameter (range 0.23-40)**
    - Chiller et al. Arch Dermatol 2000; 136:1355-9
  - Excision with **complete circumferential and deep margin assessment (CCPDMA**) by intraoperative frozen sections OR permanent sections and enface sectioning with delayed reconstruction is associated with highest rate of cure
  - **WLE with at least 2cm margins** to fascia if Mohs or CCPDMA not available or patient specific factors
- Recurrence rates after **WLE 54.5%** and **MMS 6% for primary MAC**
- **Recurrent MAC** treated with **WLE recurred in 77.8%, MMS 26.3%**

Worley B et al. Evidence-Based Clinical Practice Guidelines for Microcystic Adnexal Carcinoma. Informed by a Systematic Review. JAMA Dermatol 2019; 155: 1059-1068.

Microcystic Adnexal Carcinoma
Mohs surgery vs WLE

Yerneni S, Murad F, Schmults CD, Ruiz ES.
Improved Margin Control of Microcystic Adnexal Carcinoma After Mohs Micrographic Surgery Compared With Wide Local Excision.
Dermatol Surg 2023; 49(4):317-321.

- 27 year retrospective study of surgical outcomes (margin status after resection, recurrence outcomes including local recurrence (LR), nodal metastases (NM) and distant metastases (DM)
- 34/69 treated with MMS with clear margins, 35/69 had WLE
- 21/35 WLE (60%) had positive margins and required multiple excisions to clear
- **More MACs treated with WLE developed LR, NM or DM,** although not statistically significant
- Real-time complete margin assessment is important for this locally aggressive and infiltrative tumor.

Shayan Cheraghlou, Nicole A. Doudican, Maressa C. Criscito, Mary L. Stevenson, John A. Carucci. **Evaluating Rates of Positive Margins After Standard Excision of Cutaneous Adnexal Malignancies. Dermatol Surg 2023;49:907–913.**

TABLE 2. Rate of Margin Positivity After Standard Excision by Primary Site and Adnexal Tumor Subtype

Primary Site	Adnexal Tumor Subtype	Proportion of Cases with Positive Margins, %	SE, %
All	Microcystic adnexal carcinoma	10.8	1.5
	Eccrine adenocarcinoma	8.0	1.3
	Sebaceous carcinoma	6.0	0.5
	Apocrine adenocarcinoma	5.7	1.7
	Spiradenocarcinoma	4.2	2.1
	Hidradenocarcinoma	3.8	1.0
	Porocarcinoma	2.8	0.6
	Eccrine papillary adenocarcinoma	2.7	1.2
Head and neck	Microcystic adnexal carcinoma	11.6	1.8
	Eccrine adenocarcinoma	12.1	2.3
	Sebaceous carcinoma	7.8	0.7
	Apocrine adenocarcinoma	8.5	3.1
	Spiradenocarcinoma	3.6	3.6
	Hidradenocarcinoma	5.6	2.2
	Porocarcinoma	5.8	1.8
	Eccrine papillary adenocarcinoma	—	—
Trunk and extremity	Microcystic adnexal carcinoma	8.0	2.9
	Eccrine adenocarcinoma	4.7	1.3
	Sebaceous carcinoma	3.1	0.6
	Apocrine adenocarcinoma	3.7	1.8
	Spiradenocarcinoma	4.4	2.5
	Hidradenocarcinoma	3.1	1.1
	Porocarcinoma	1.8	0.6
	Eccrine papillary adenocarcinoma	2.8	1.2

- National Cancer Database 2004-2019
- 4402 adnexal carcinomas treated with WLE vs NLE
- Tumors on HN were 2x more likely than non HN tumors to have positive margins
  - Eccrine adenocarcinoma HN 12.1%
  - MAC HN 11.6%, T&E 8.0%,
  - **Positive margins associated with poorer overall survival on multivariable survival analysis**
- Adnexal carcinomas on HN and some on T&E should be considered for MMS

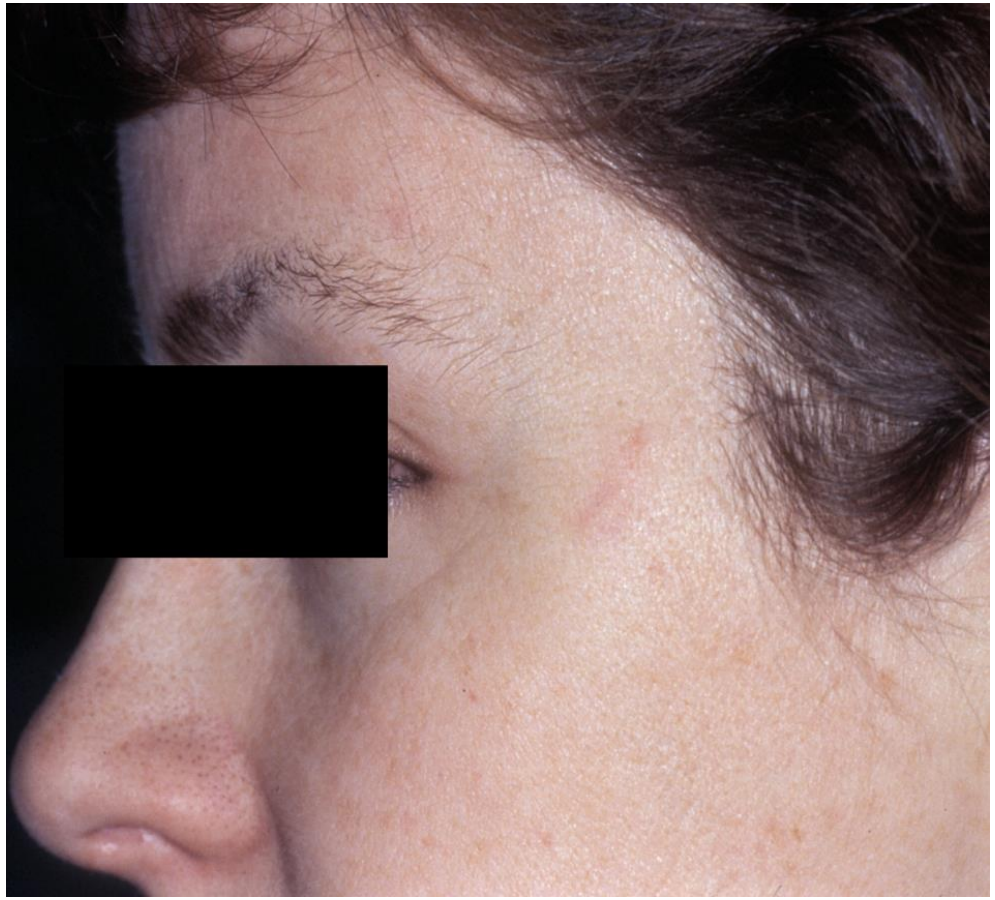
Microcystic Adnexal Carcinoma
Evaluation and Management

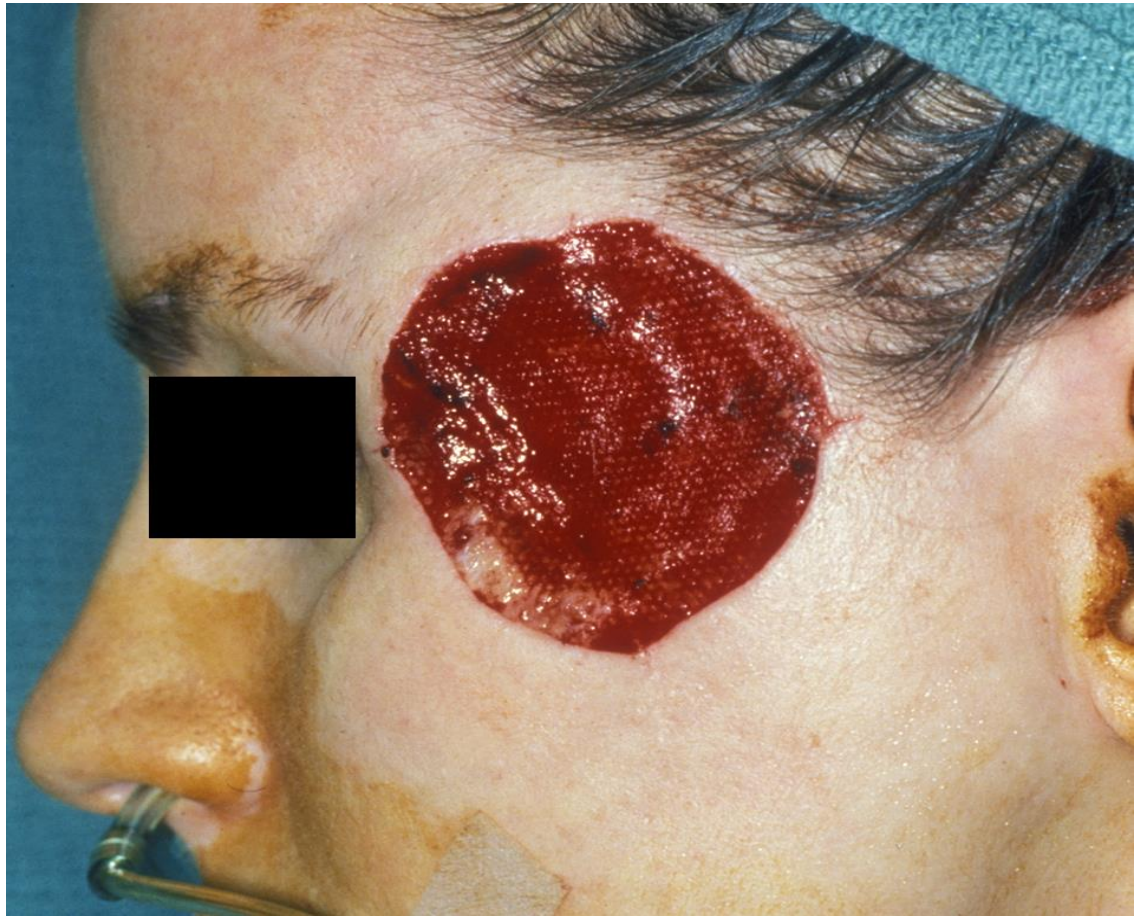
- Radiotherapy (RT)
  - Not a preferred first line therapy due to limited clinical evidence
  - May be considered for nonsurgical candidates
  - Adjuvant RT may be considered for recurrent tumors, incompletely excised tumors, or on an individual basis for those thought to be at high risk for recurrence
  - Neoadjuvant XRT
    - Neoadjuvant Radiation to Facilitate Surgical Treatment of a Microcystic Adnexal Carcinoma with Perineural Invasion of the Vulvar Region.

      William J. Nahm, Stanley Chen, Saiyan Joseph, Paul Chu, Jane Yoo. JAAD Case Reports 2023;38:72-4
- Regional LN and distant metastases occur rarely, best treatment unclear
  - Nodal radiotherapy for MAC metastatic disease not recommended
  - Chemotherapy or immunotherapy for distant metastases is not recommended

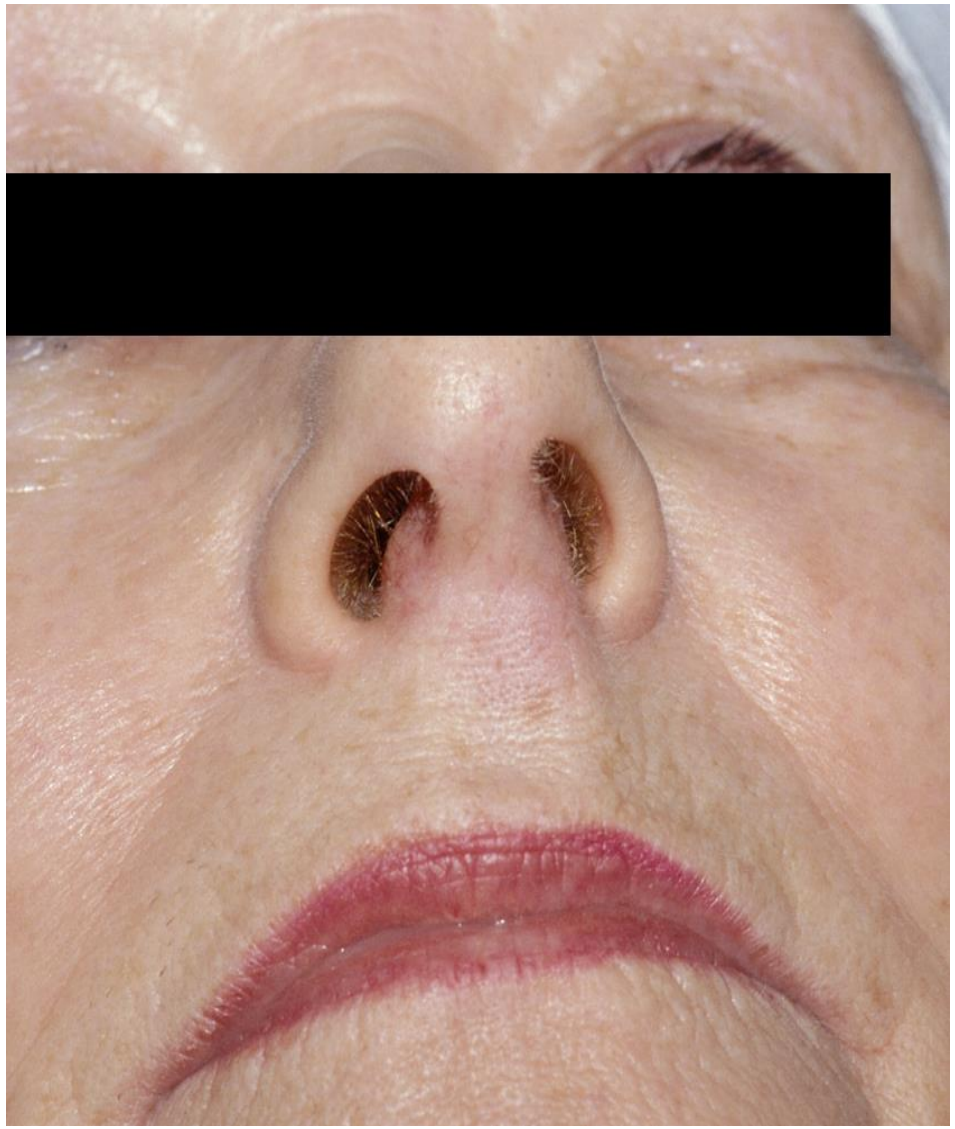
Worley B et al. Evidence-Based Clinical Practice Guidelines for Microcystic Adnexal Carcinoma. Informed by a Systematic Review. JAMA Dermatol 2019; 155: 1059-1068.

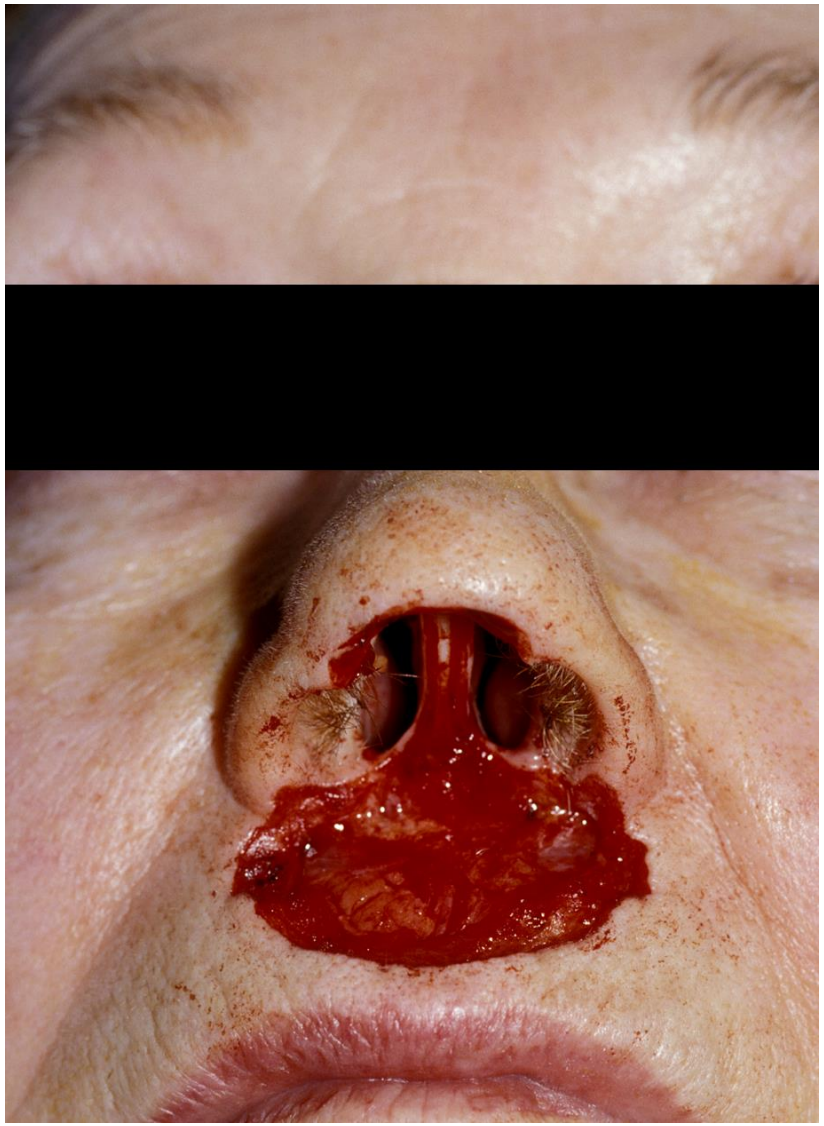
MAC





MAC





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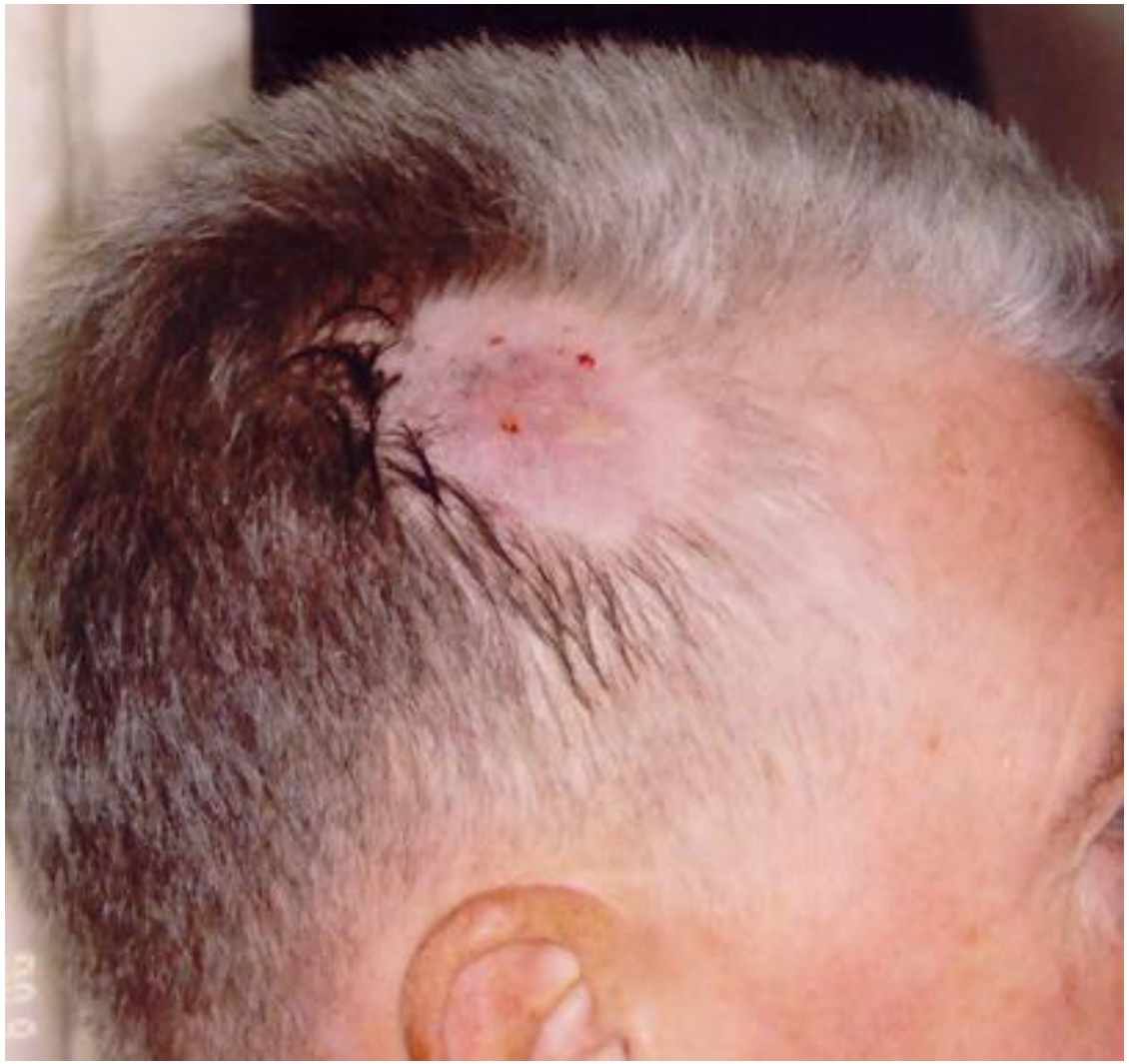
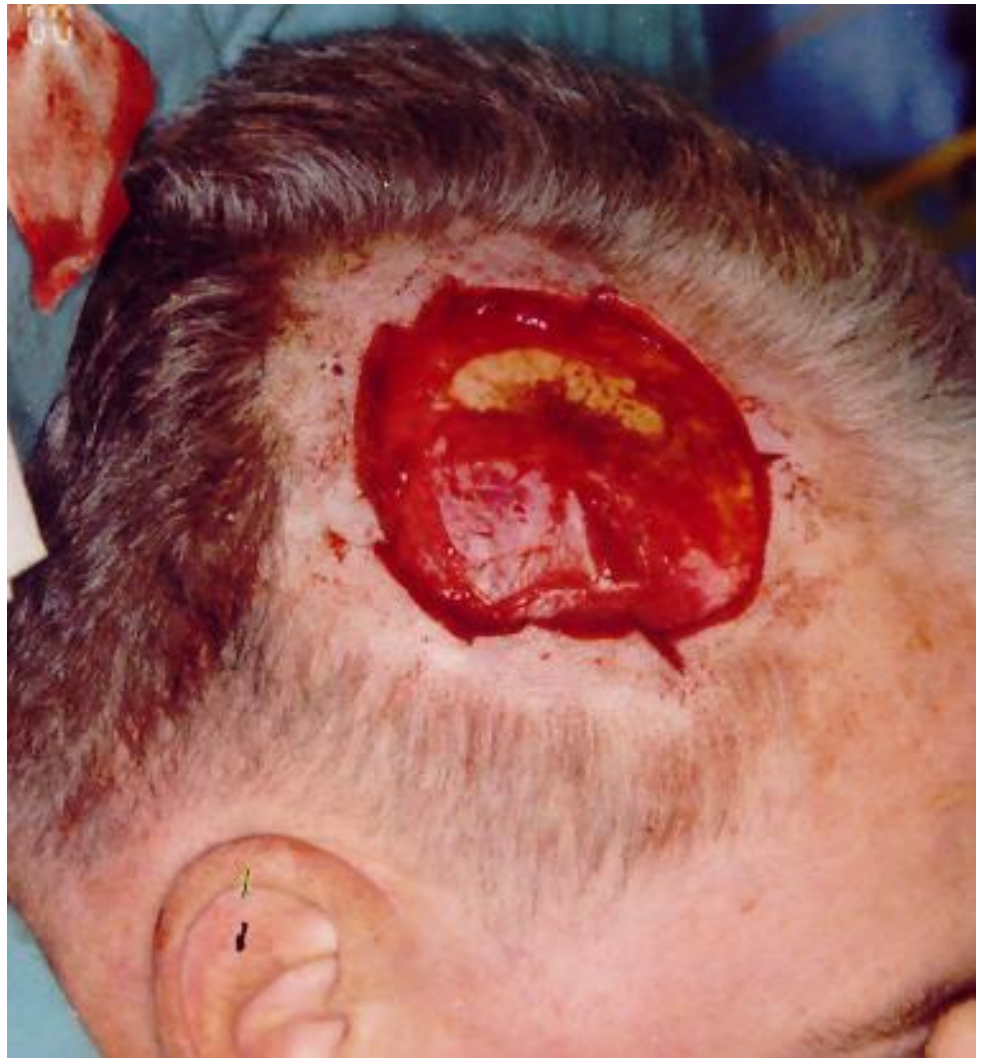




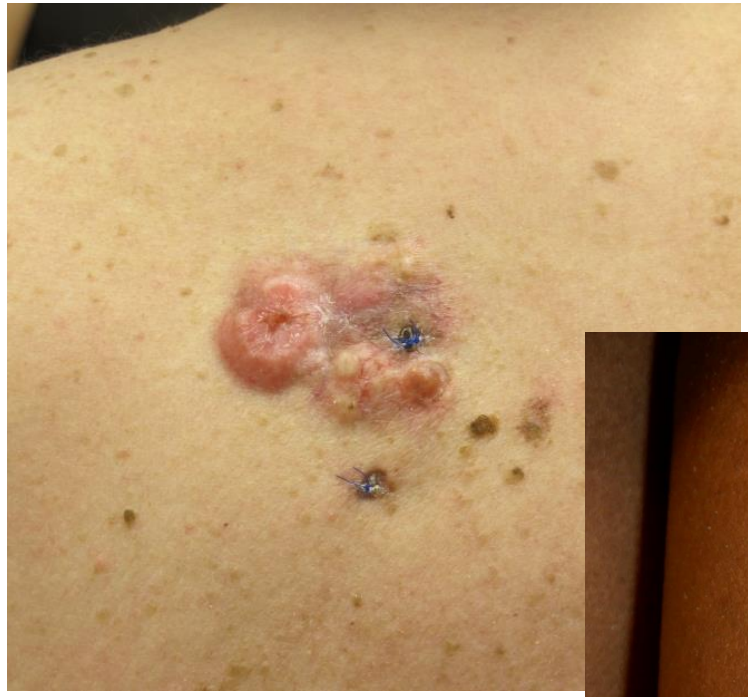
Callahan EF, Vidimos AT, Bergfeld WF. Microcystic Adnexal Carcinoma of the scalp with extensive pilar differentiation. Dermatol Surg 2002; 28: 536-9.

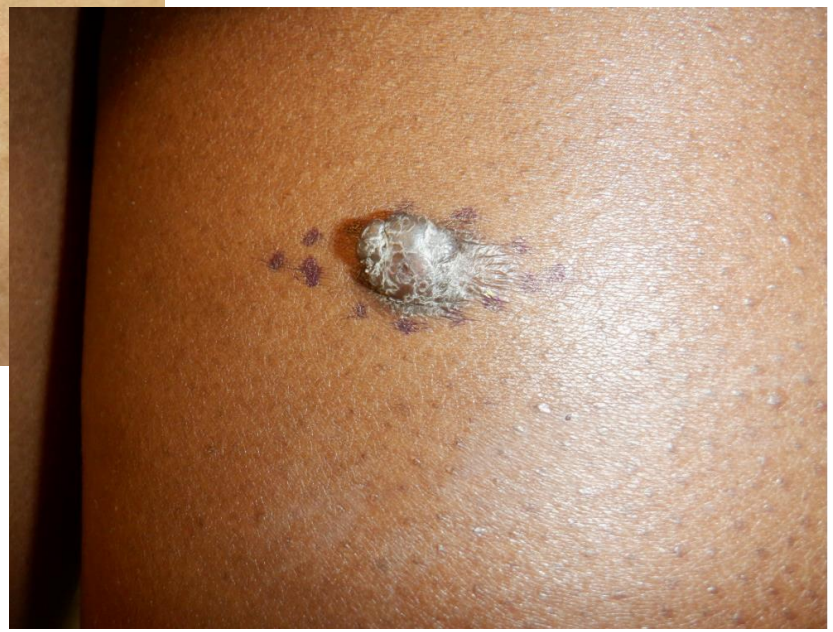
Microcystic Adnexal Carcinoma Follow- Up

- History and FBSE and LN exam every 6-12 months for 5 years, yearly thereafter
- Monthly self skin exams
- Educate patient on scar maturation and changes in sensation around scar
- Consider periodic US of LN basin in patients with positive LN or at high risk for nodal spread every 6-12 months

Dermatofibrosarcoma Protuberans (DFSP)

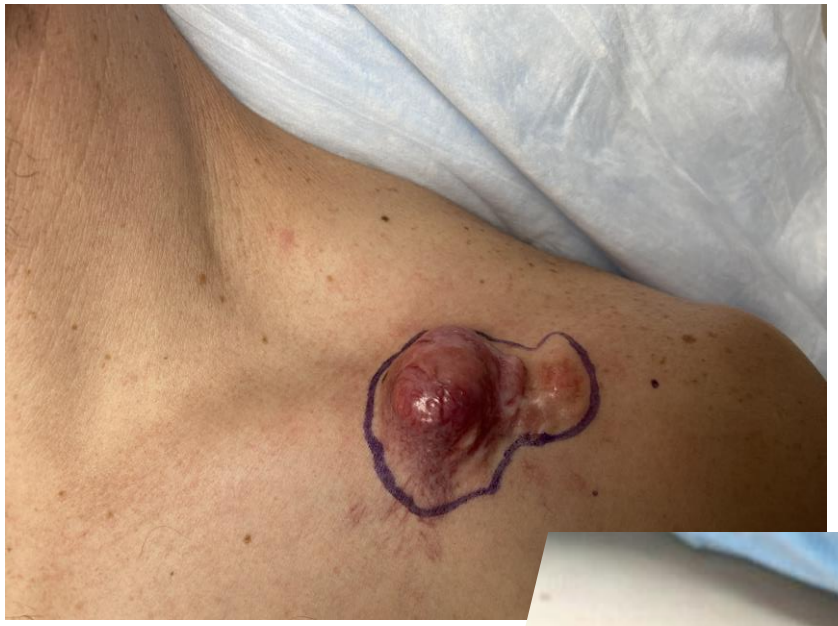
- Intermediate grade fibrohistiocytic sarcoma
- 1-6% of all soft tissue sarcomas, 18% of all cutaneous soft tissue sarcomas
- Extensive local infiltration, and rare distant mets (LN, lung)
- Slow growing firm nodule or plaque
  - Flesh colored
  - Red
  - Blue
- Sites: Trunk > extremities, H & N (15% scalp and supraclavicular fossa)

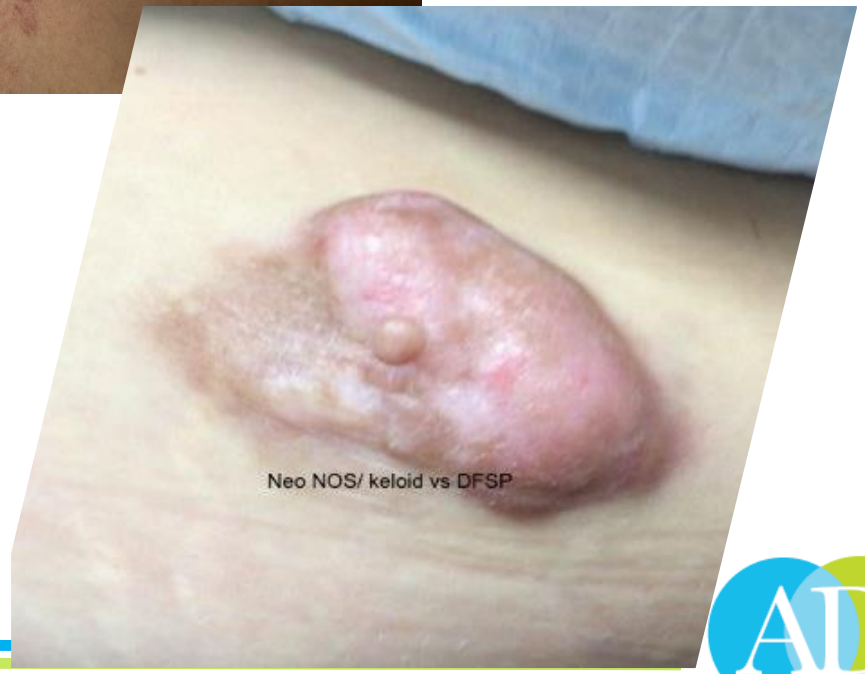




DFSP

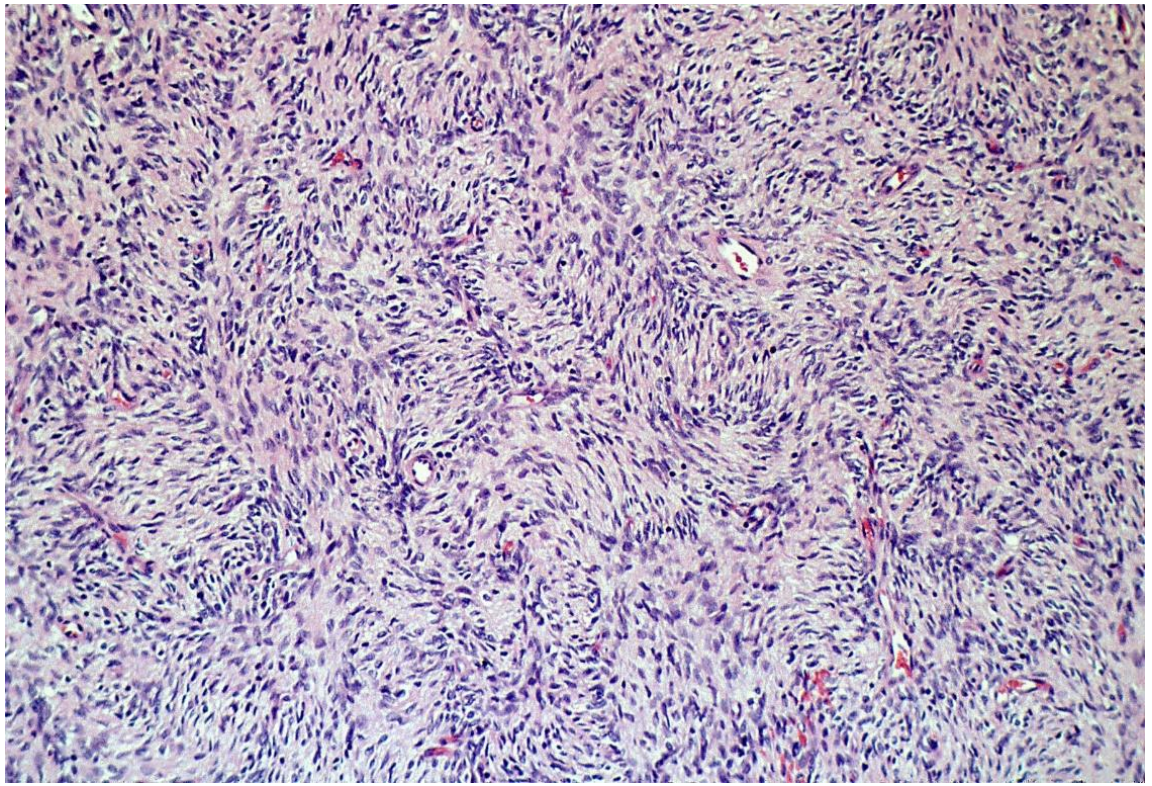
- M > F, 20-59 y.o.
- Highest incidence in African Americans
- Association noted with traumatic and surgical scars, burns
- 5 year relative survival rate =91-100%
- <5% risk of metastases (with fibrosarcomatous change. higher risk of recurrence and mets)
- Risk factors for higher mortality rates: high mitotic index, increased cellularity, black race, male sex, location on HN or limb





DFSP
Histology

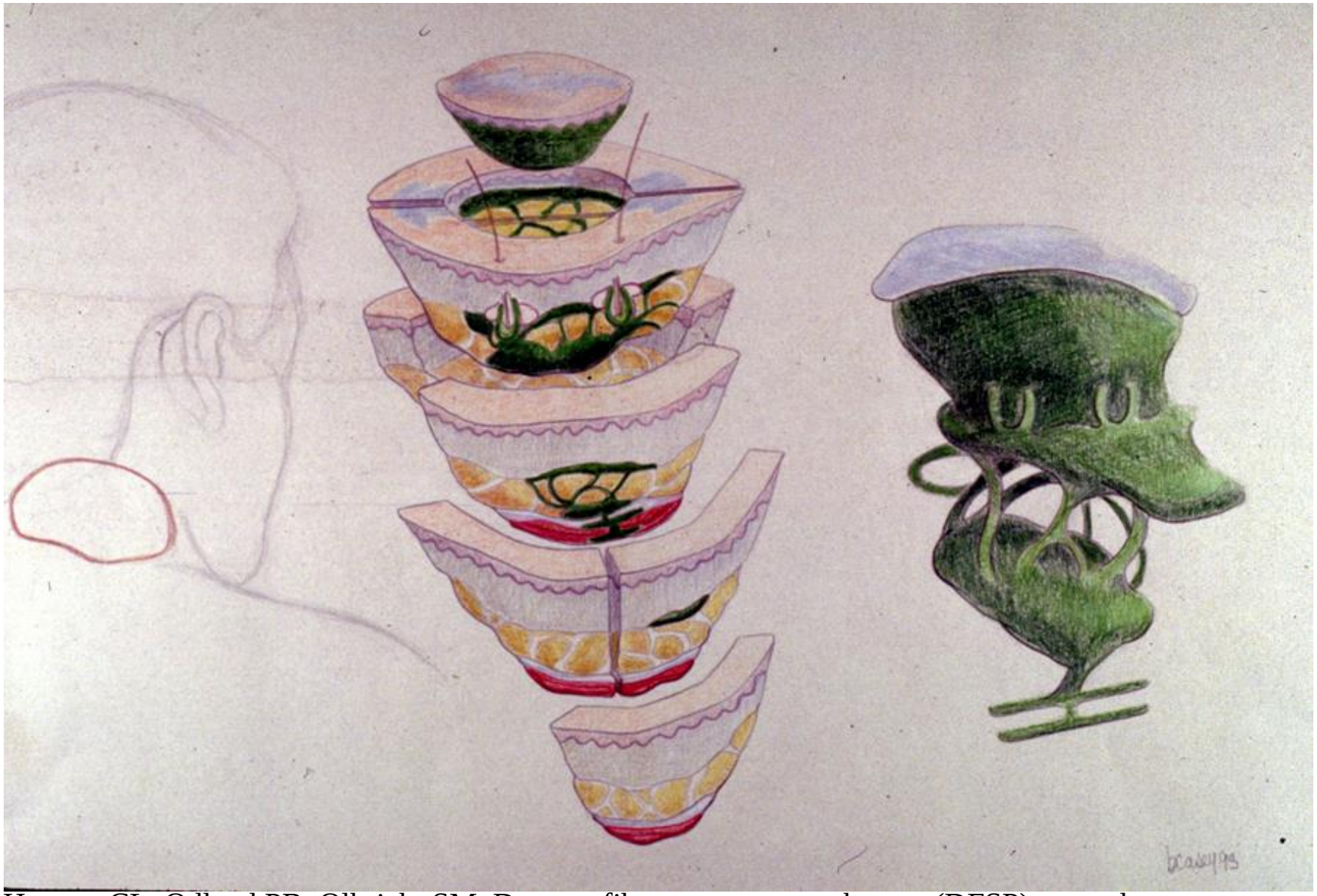
- Uniform population of spindle cells in storiform “cartwheel” pattern, honeycomb infiltration into fat; low to moderate mitotic activity
- CD34+, Factor XIII a negative; IHC 84-100% sensitive
- Histopathologic variants: Bednar, myxoid, atrophic, fibrosarcomatous, mixed, granular cell and sclerosing
- 10-15% of DFSP have areas of fibrosarcomatous transformation which is associated with more aggressive clinical course



Genetic Defect
DFSP

- >90% of DFSP have characteristic chromosomal translocation t(17;22)(q22;q13) which results in fusion of the collagen type 1 alpha 1 gene (COLA1A) to the platelet derived growth factor beta chain gene-(PDGFb)

- The COL1A1-PDGFb fusion transcript leads to the continuous activation of the PDGFb receptor, promoting the proliferation of DFSP tumor cells



Haycox CL, Odland PB, Olbricht SM. Dermatofibrosarcoma protuberans (DFSP): growth Characteristics based on tumor modeling and a review of cases treated with Mohs micrographic surgery. Ann Plast Surg 1997; 38: 246-251.

DFSP with fibrosarcomatous change (DFSP- FS)

- DFSP-FS is a distinct subtype of DFSP
  - A higher degree of cellularity, cytologic atypia, mitotic activity, and negative CD34 immunostaining
  - 10-15% of DFSP have FS areas
- NO differences in age, gender, location, clinical appearance, previous trauma or presentation status between DFSP and DFSP-FS
- FS change more common in **recurrent** tumors
- More recent reports indicate poorer prognosis with fibrosarcomatous DFSP

DFSP-FS

	Recurrence rate	Metastatic rate
DFSP	1.7-41%	4-5%
DFSP-FS	58.5%	12.1%
FS	18-79%	63% at 5 years

Case series of 27 DFSP, 4 were DFSP-FS
Literature review 41 DFSP-FS cases
Distant mets from DFSP-FS have occurred up to **6 years** after wide excision

Am J Dermatopathol 1997; 19: 562-7.

- St. Martin EC et al. **Dermatofibrosarcoma protuberans Recurrence After Wide Local Excision Versus Mohs Micrographic Surgery: A Systematic Review and Meta-Analysis.** Dermatol Surg 48:479-485, 2022

  - 88 studies met inclusion criteria 1946-2018 (12 comparative, 76 single arm studies)
  - **Comparative studies**
    - 352 patients had MMS and 777 had WLE
    - Local recurrence rate
      - **MMS 1.7%**
      - **WLE 3.7%**
  - **Noncomparative studies**
    - 980 patients had MMS and 2215 had WLE
    - Local recurrence rate
      - **MMS 1.5%**
      - **WLE 9.4%**
  - **MMS should be strongly considered when available for DFSP**

Crum OM et al. **Disease-specific Mortality of Dermatofibrosarcoma Protuberans After Mohs Surgery Versus Wide Local Excision: A Systematic Review and Meta-analysis. Dermatol Surg 2024; 50:317-21.**

- Systematic literature search, 136 studies
- Disease specific mortality rate was NOT significantly different after treatment with MMS vs WLE for **primary** DFSP
- Disease specific mortality was statistically significantly **lower** with MMS (1%) vs WLE (3.5%) for **recurrent** DFSP
- Mean follow up was 57.6 months

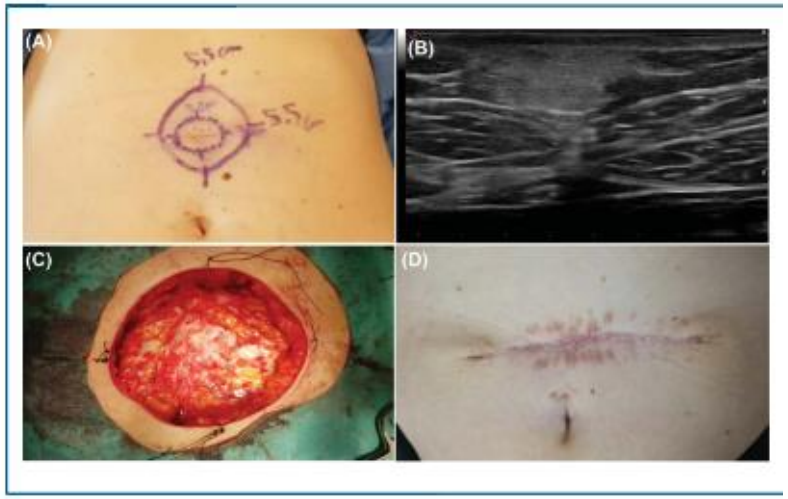
Treatment
DFSP

- **XRT** mostly used as **adjunct** after surgery for positive margins
- **Imatinib** – oral tyrosine kinase inhibitor, FDA approved 2006 for unresectable or metastatic DFSP, 400-800mg/day
  - Navarrete-Dechent C et al. Imatinib treatment for locally advanced or metastatic dermatofibrosarcoma protuberans. JAMA Dermatol 2019;155: 361-369
    - 9 studies, 152 patients
    - **CR 5.2%, PR 55.2%, stable disease 27.6%, progression 9.2%**
    - No difference in 400mg and 800mg/day
  - **Neoadjuvant use** in large DFSP or tumors in functionally or cosmetically crucial areas
    - Average tumor shrinkage 36-40% .
      - J Med Case Rep 2019;13:374.

Preoperative imaging DFSP

- Large tumor size
- Tumors with suspected deeper component
- Recurrent tumors
- Critical anatomic locations
- Re-excision of DFSPs with positive surgical margins
- **MRI**
- PET CT – mild uptake FDG
  - Riggs K et al. Dermatol Surg 2009; 35: 2036-2041

- Intraoperative ultrasound may help delineate margins
  - Sanchez-Diaz M et al Dermatol Surg 2022; 48:575-77



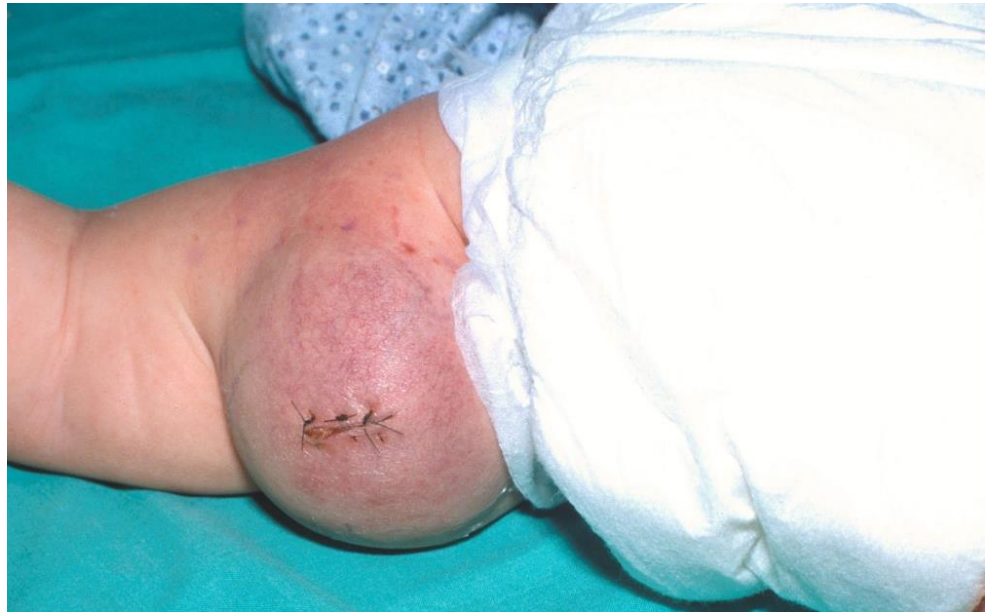
- Different sonographic presentations of dermatofibrosarcoma protuberans. Wittle C et al J Ultrasound 2024 Mar;27(1):61-65.

Childhood DFSP

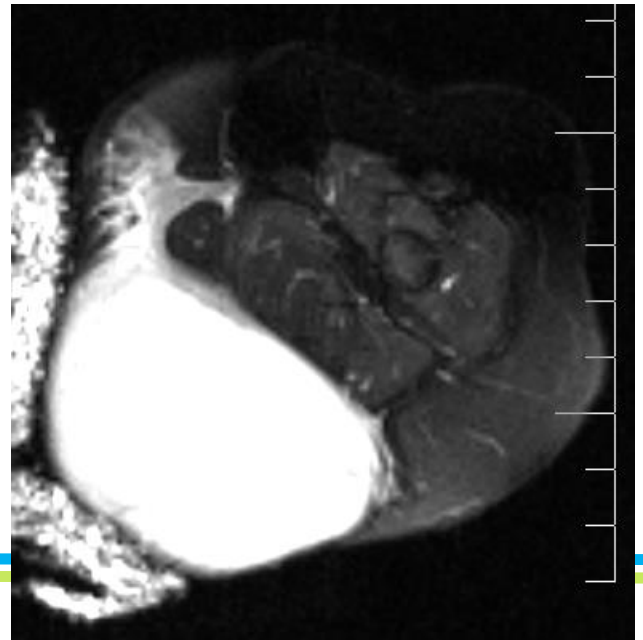
- Thornton SL, Reid J, Papay FA, Vidimos AT.

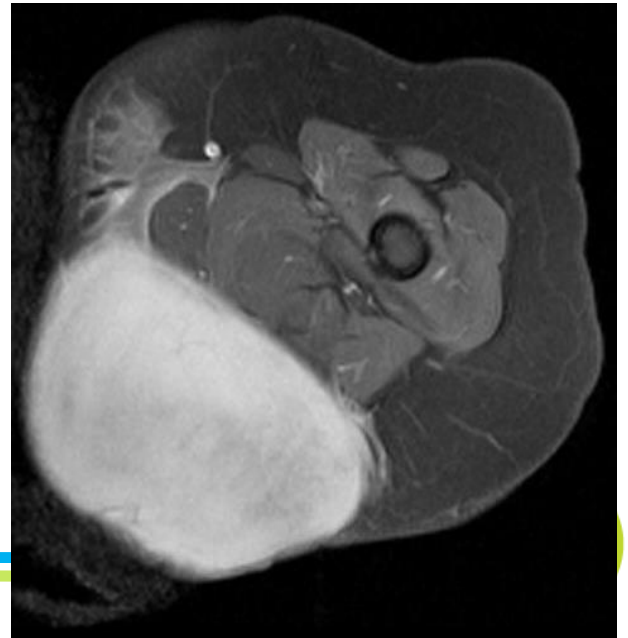
  Childhood dermatofibrosarcoma protuberans: role of preoperative imaging.

  J Am Acad Dermatol 2005; 53: 76-83.



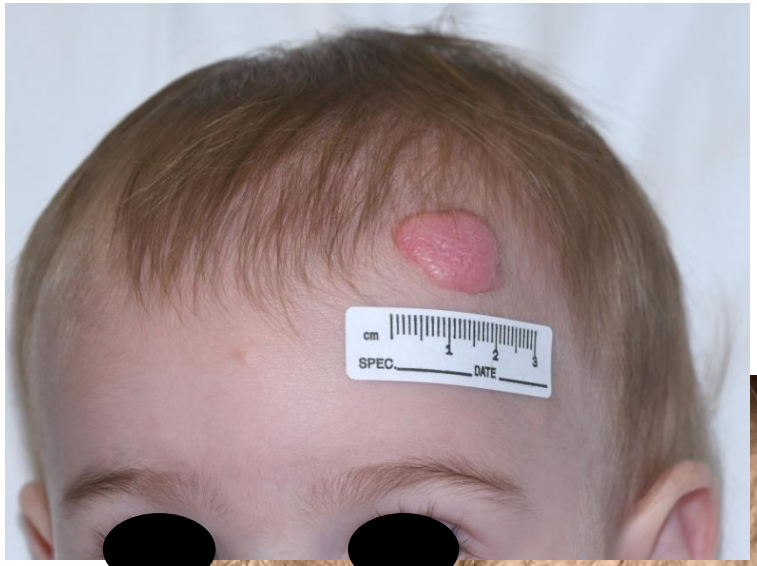
- 10 cases DFSP ages 8 months to 16 years
- **5 congenital**
- 5 had preoperative MRI which facilitated surgical planning

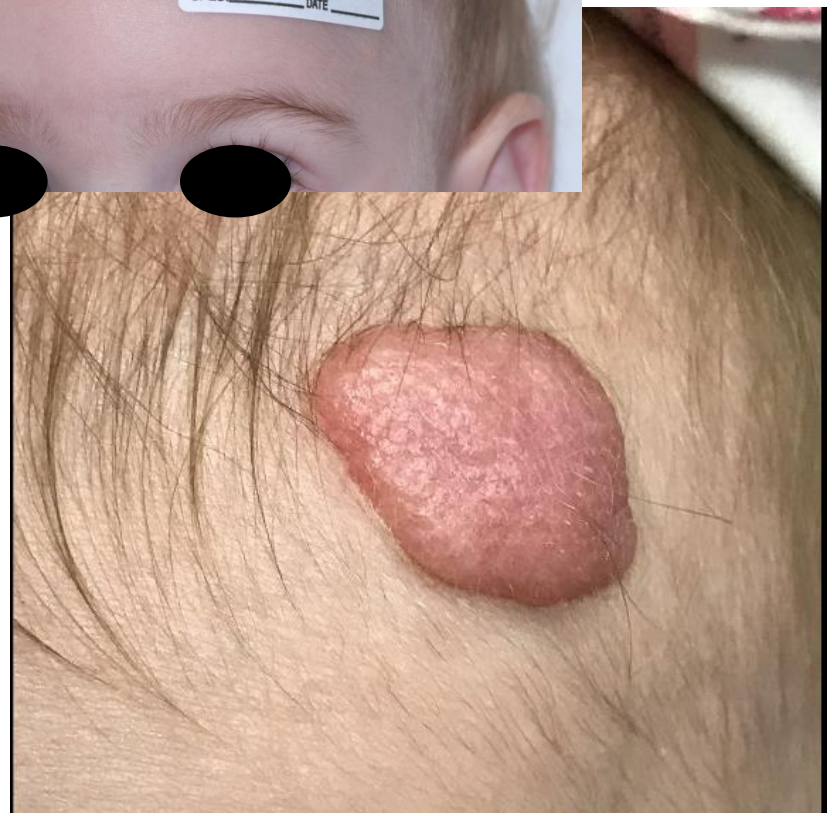




History - BD

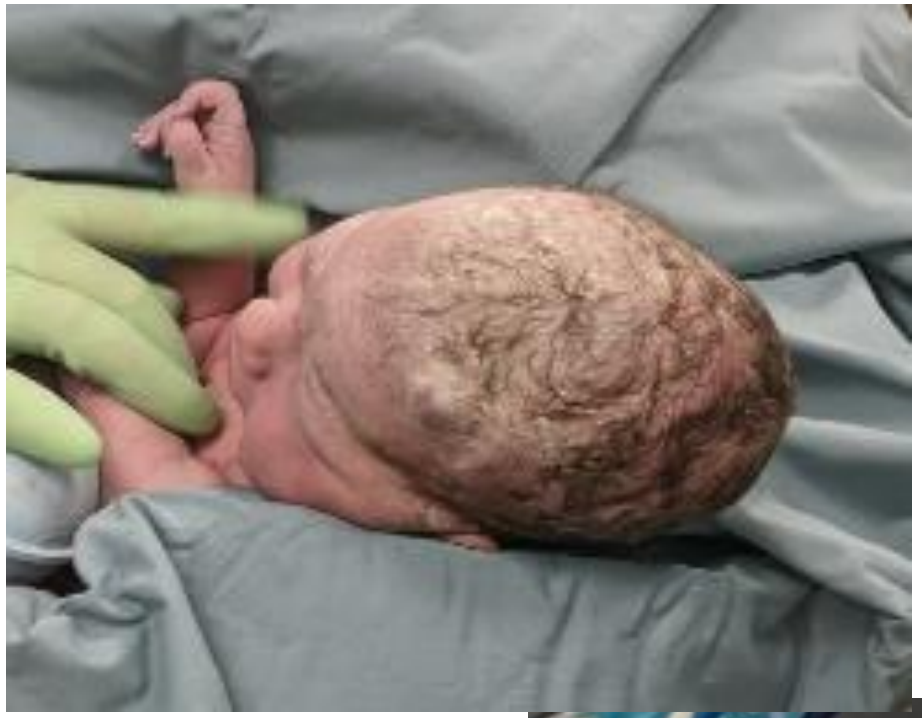
- 9 month old baby girl with congenital nodule left parietal scalp, born 10-29-20 forceps delivery
- Biopsy 5-27-21 by outside dermatologist – spindle cell tumor CD34+
- FISH for PDGFB/COLA1A was negative
- PLEKHH2-ALK gene fusion

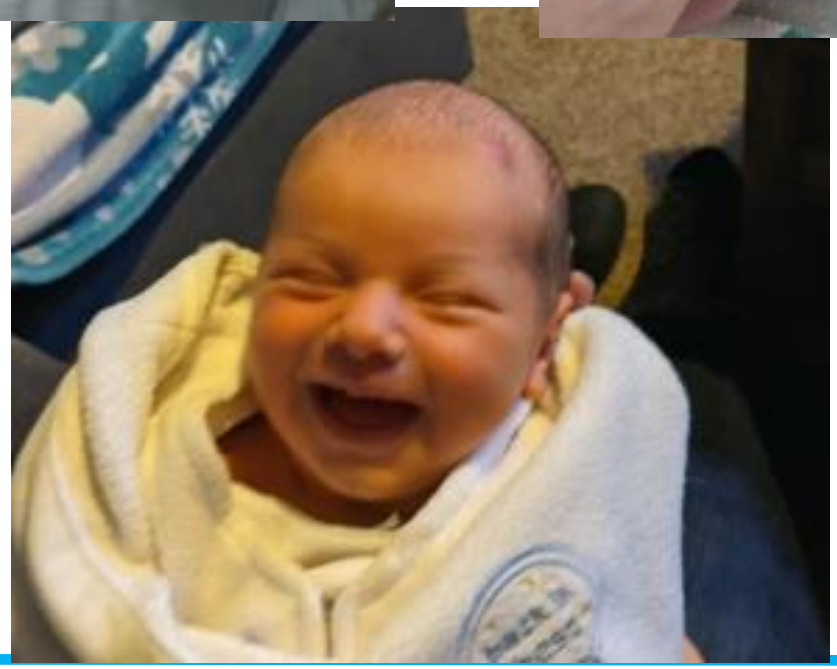




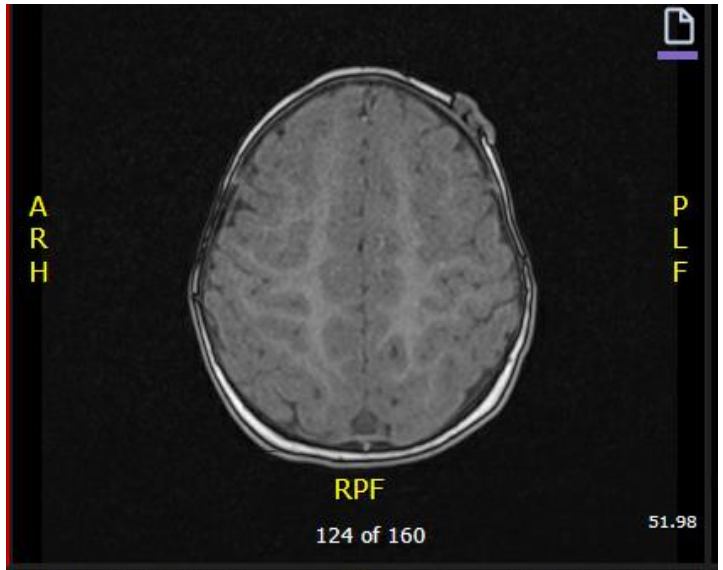
August 2021

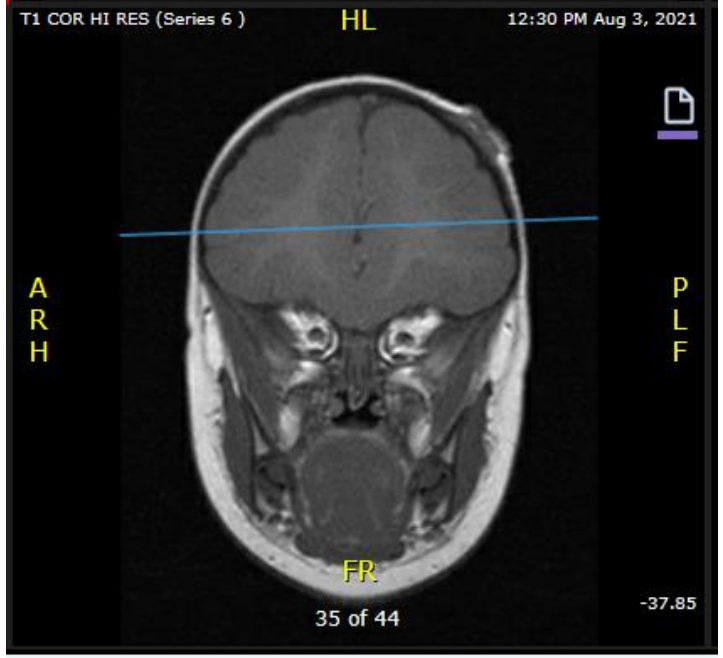
Ward RE, Stultz TW, Billings SD, Vidimos AT. Mohs Micrographic Surgery for Congenital Scalp Dermatofibrosarcoma Protuberans With Novel PLEKHH2-ALK Gene Fusion. Dermatol Surg. 2023

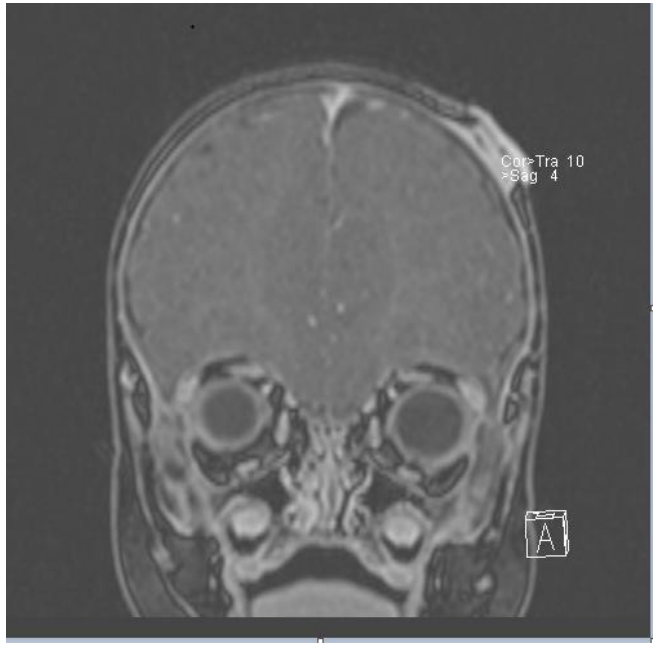




10/29/2020



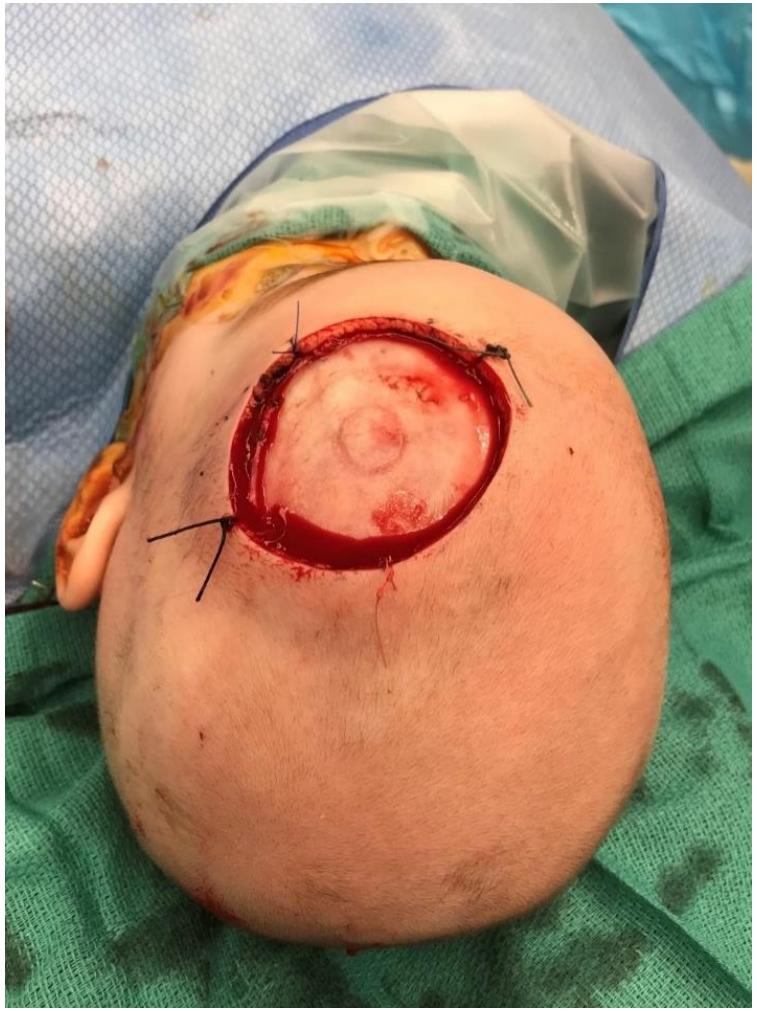


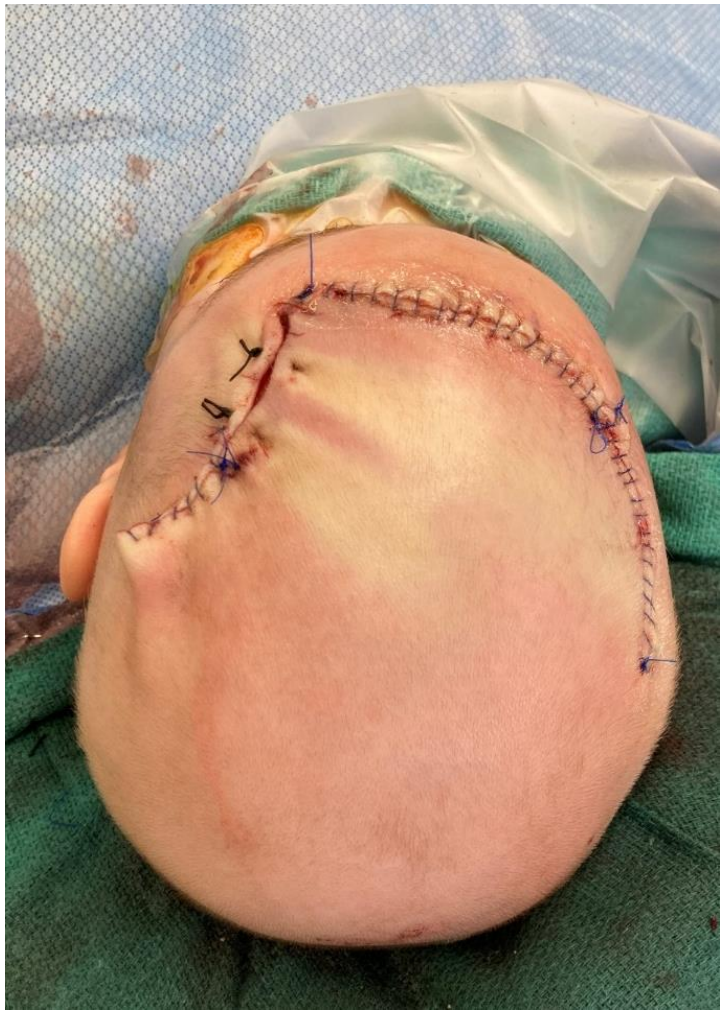


MRI brain 8-3-21

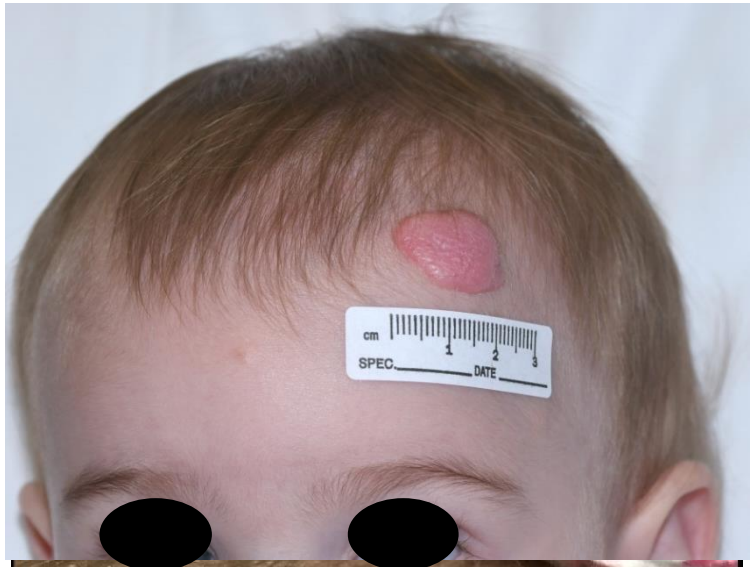
Neoplasm: Lobulated scalp lesion overlying the frontal bone to the left of midline near the vertex with mildly hyperintense T1 and T2 signal. The lesion avidly enhances and measures 2.0 x 0.9 x 1.5 cm (AP, transverse and craniocaudal dimensions), with **transosseous extension** through the subjacent frontal bone. Additionally there is **thickening/enhancement of the underlying dura suggestive of dural involvement spanning approximately a diameter of 3 cm.** There is no evidence of frank intraparenchymal brain invasion. No abnormal leptomeningeal enhancement.

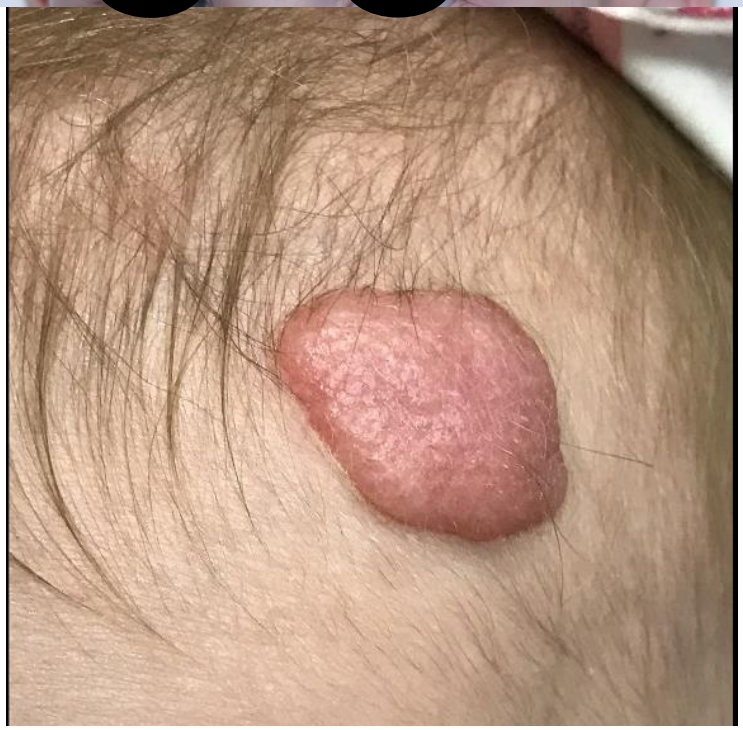
CT chest 8-19-21 and 10-19-21– stable 1mm nodule LLL, prominent subcentimeter bilateral axillary LAD





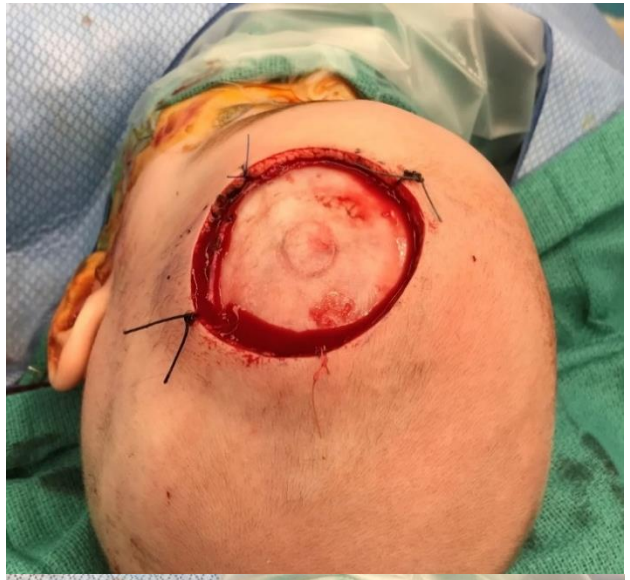
A layer 1.5cm margin to periosteum positive circumferentially and deep
B layer 1cm margin to bone clear, small area of outer table removed – no tumor
Nonmarginal tissue sent for paraffin sections- **no fibrosarcomatous change 8-24-21**

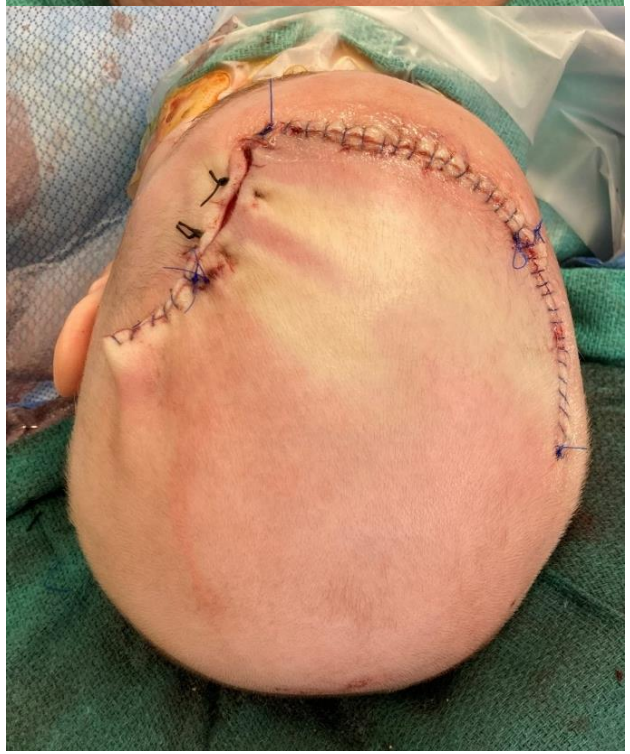




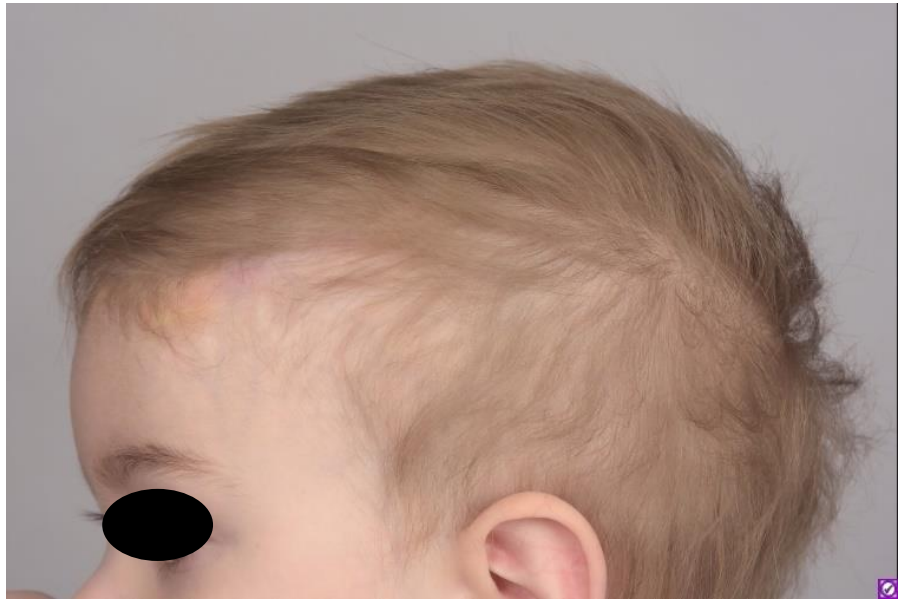
9 month old girl with congenital DFSP

August 2021

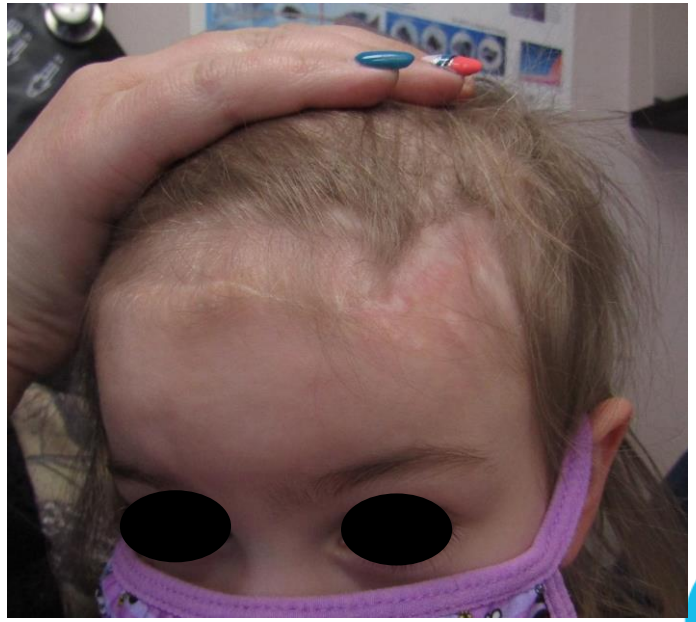




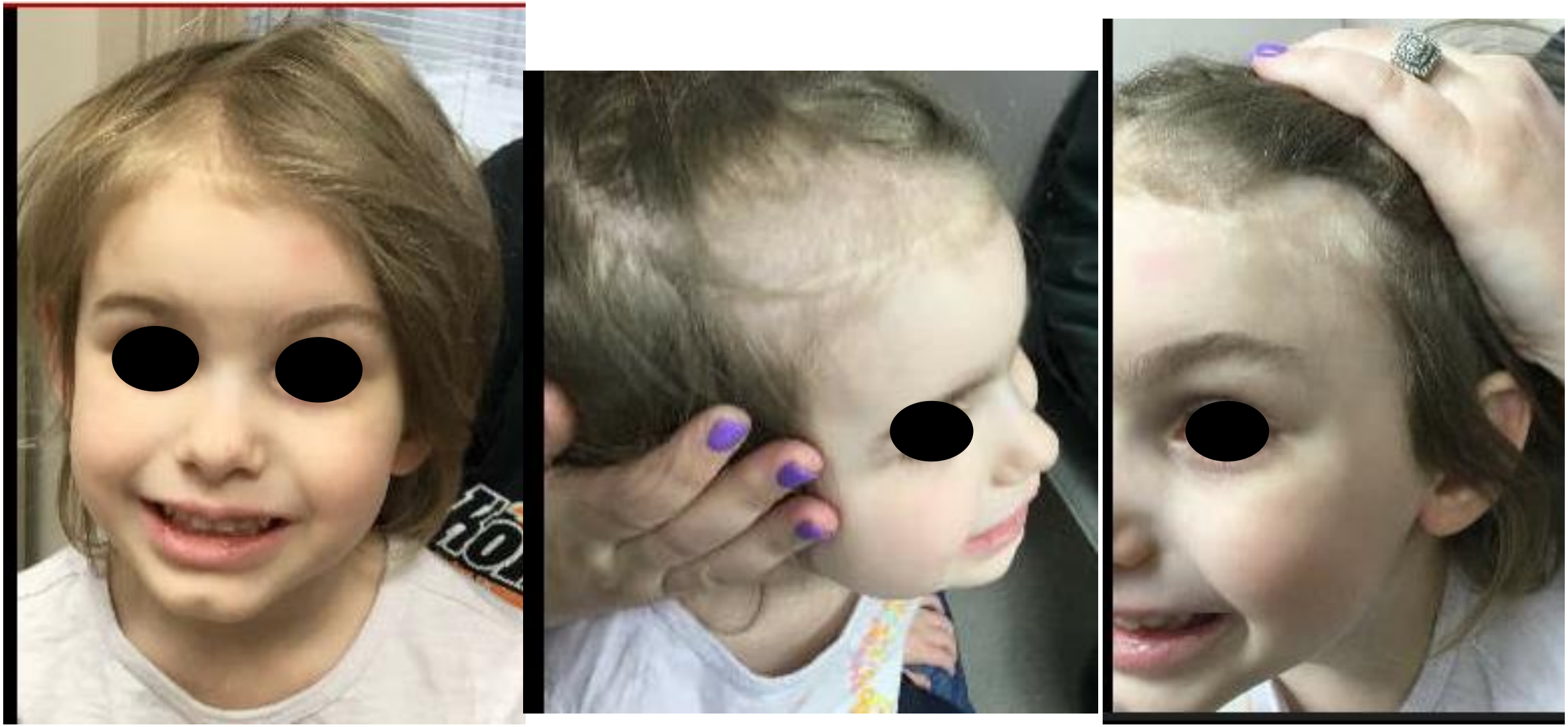
8-24-21



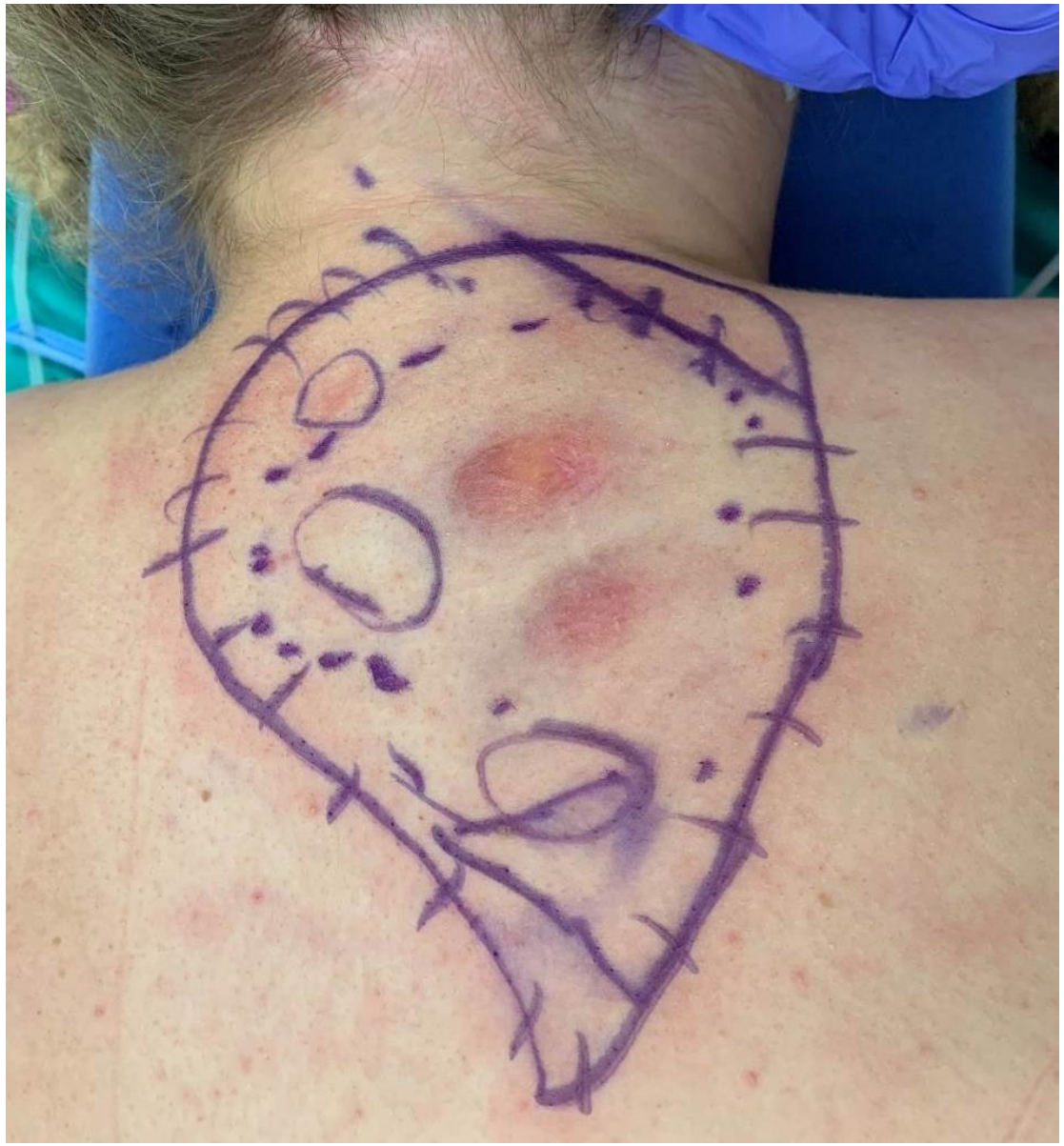
1-18-22



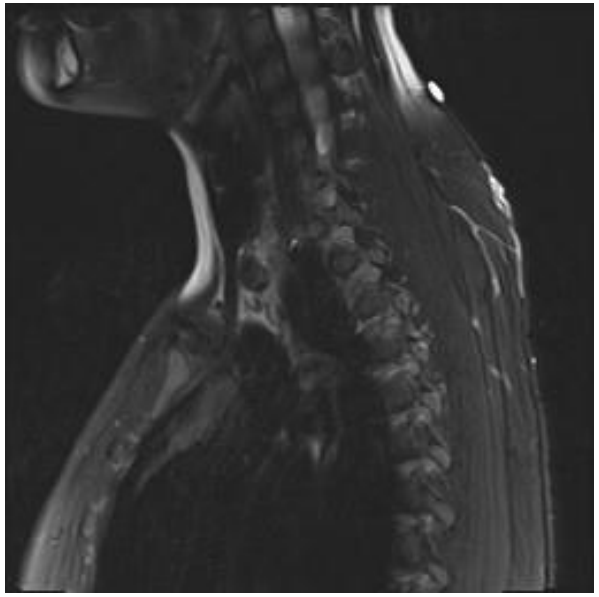
3-15-23

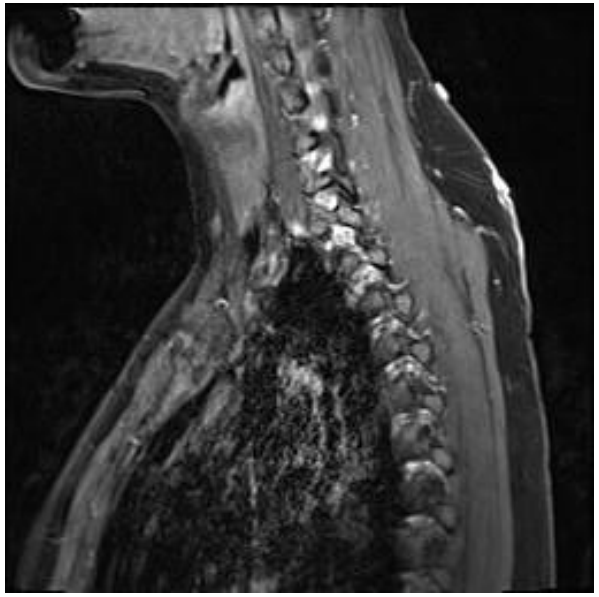


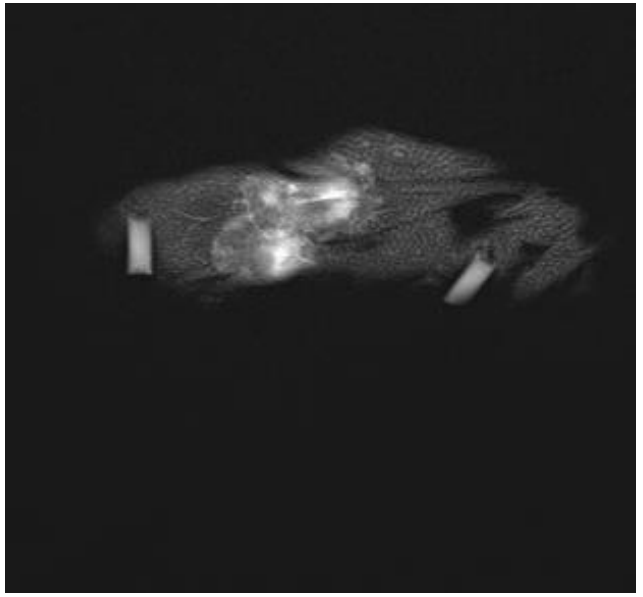
March 20, 2024
31 months postop



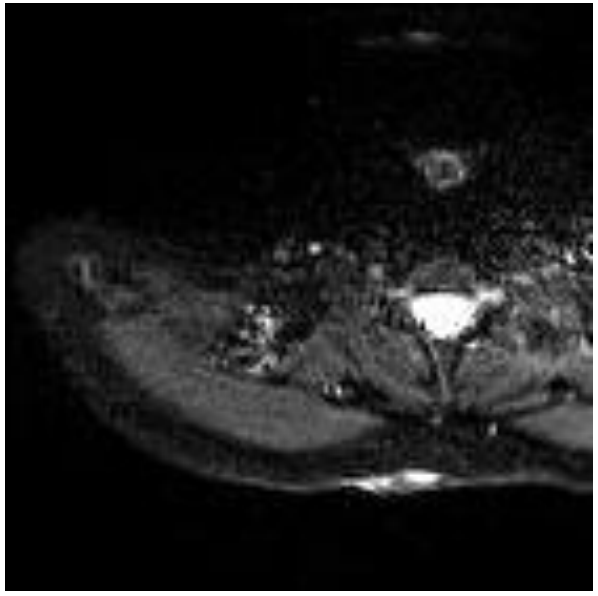
17 year old female with congenital DFSP back/neck



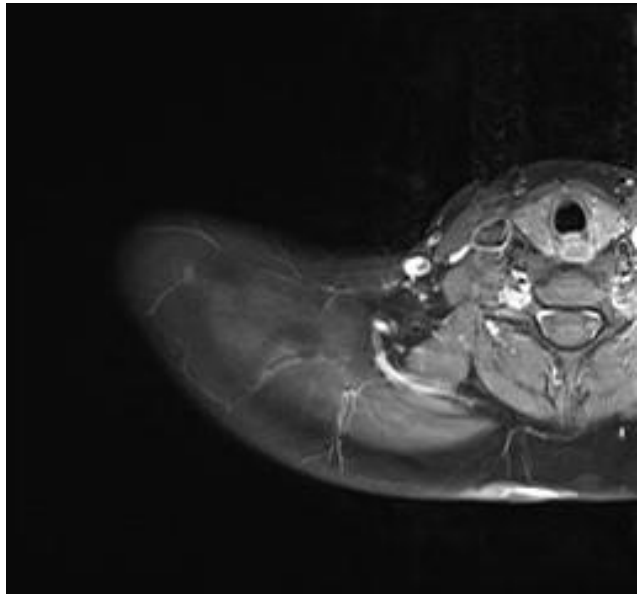




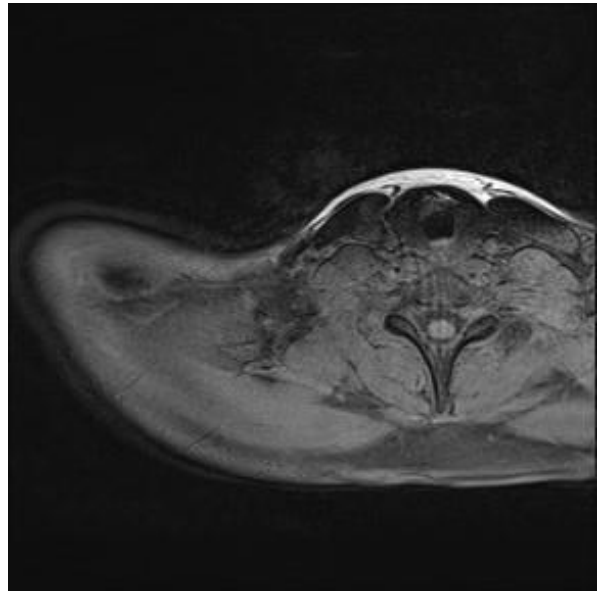
FS T2
Coronal



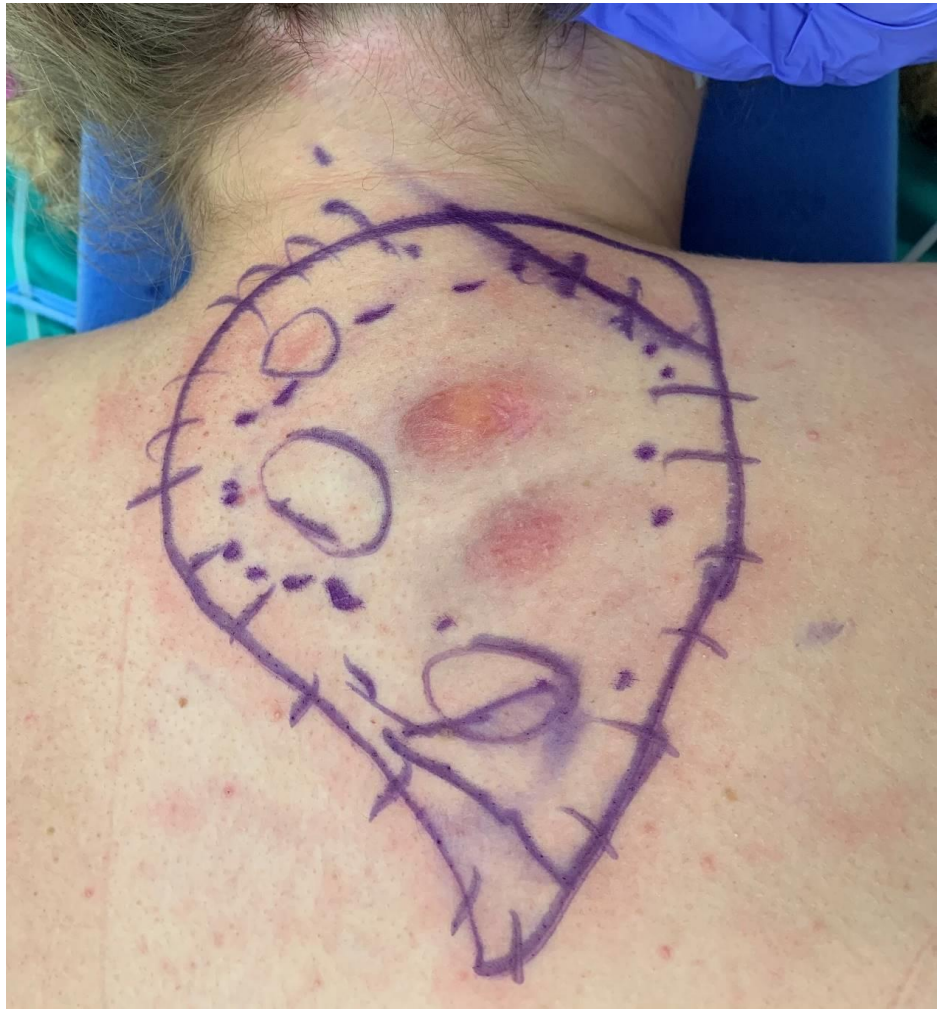
FS T2



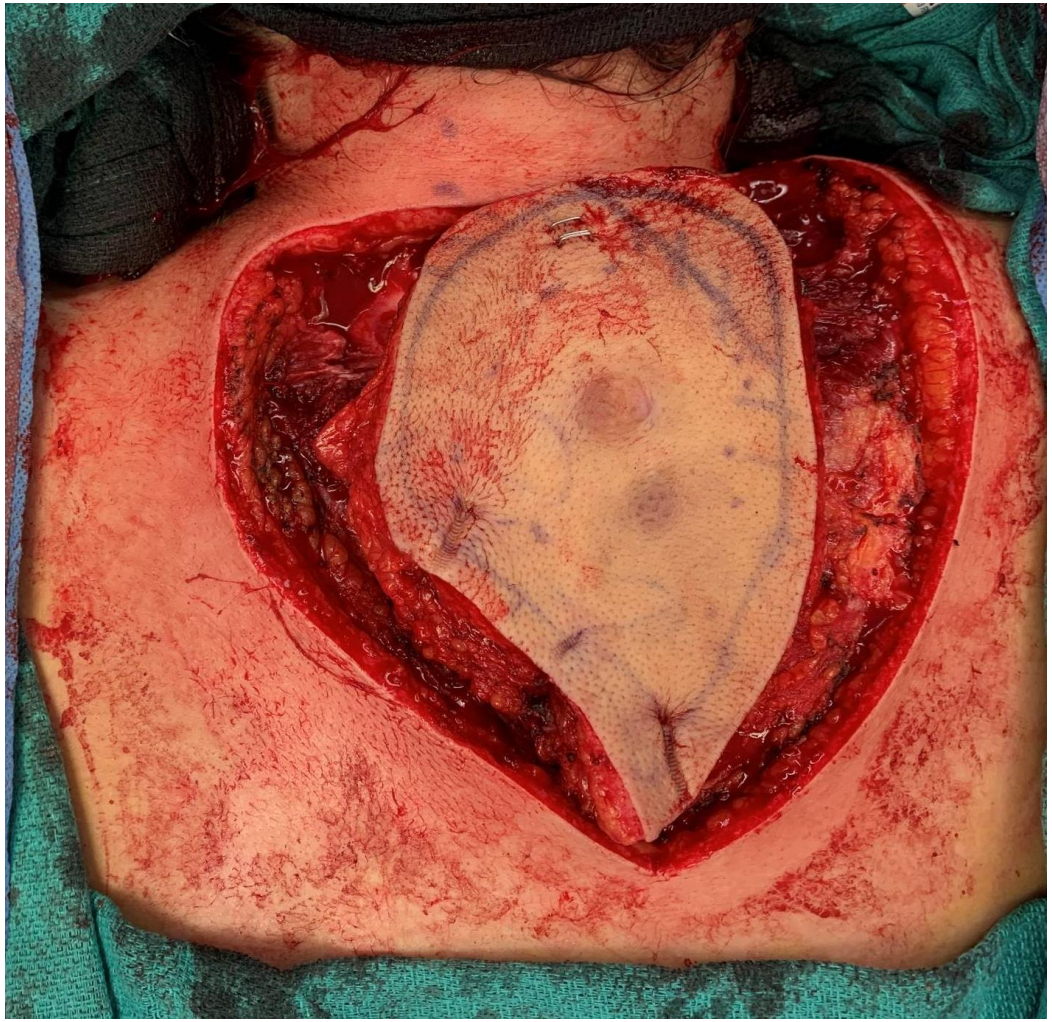
FS T1gad



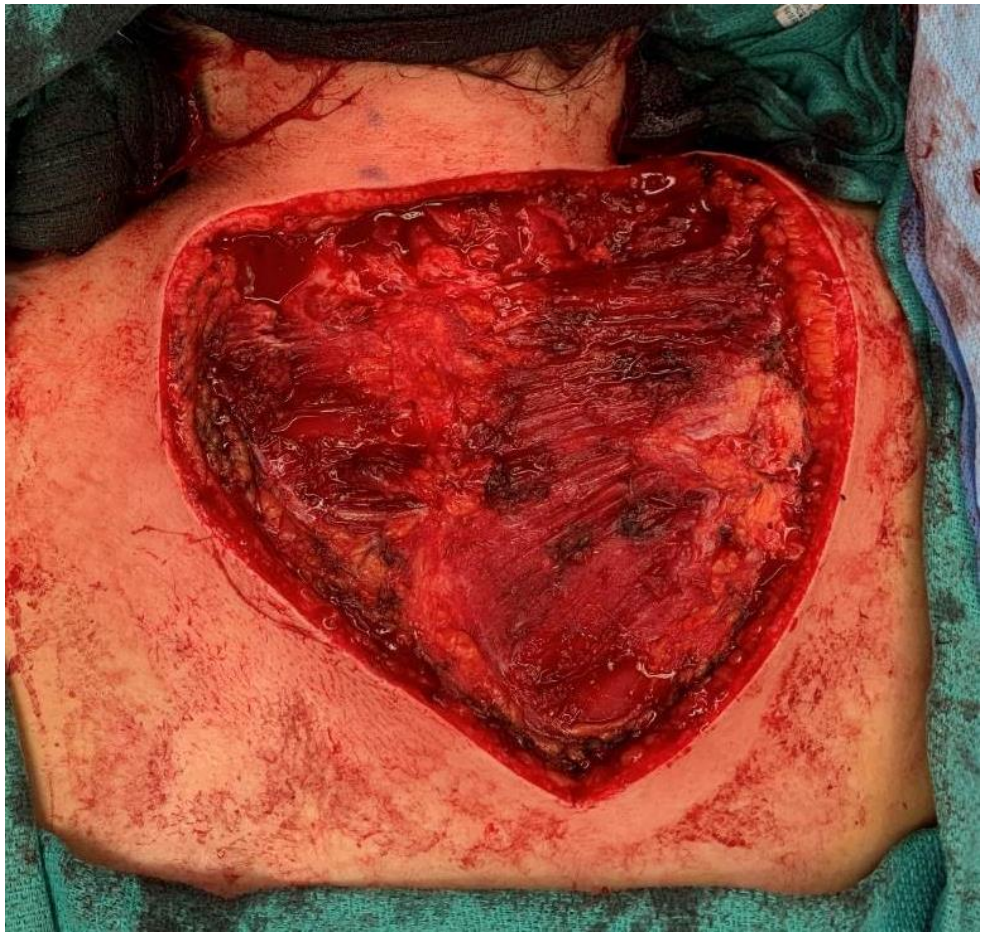
FS T1

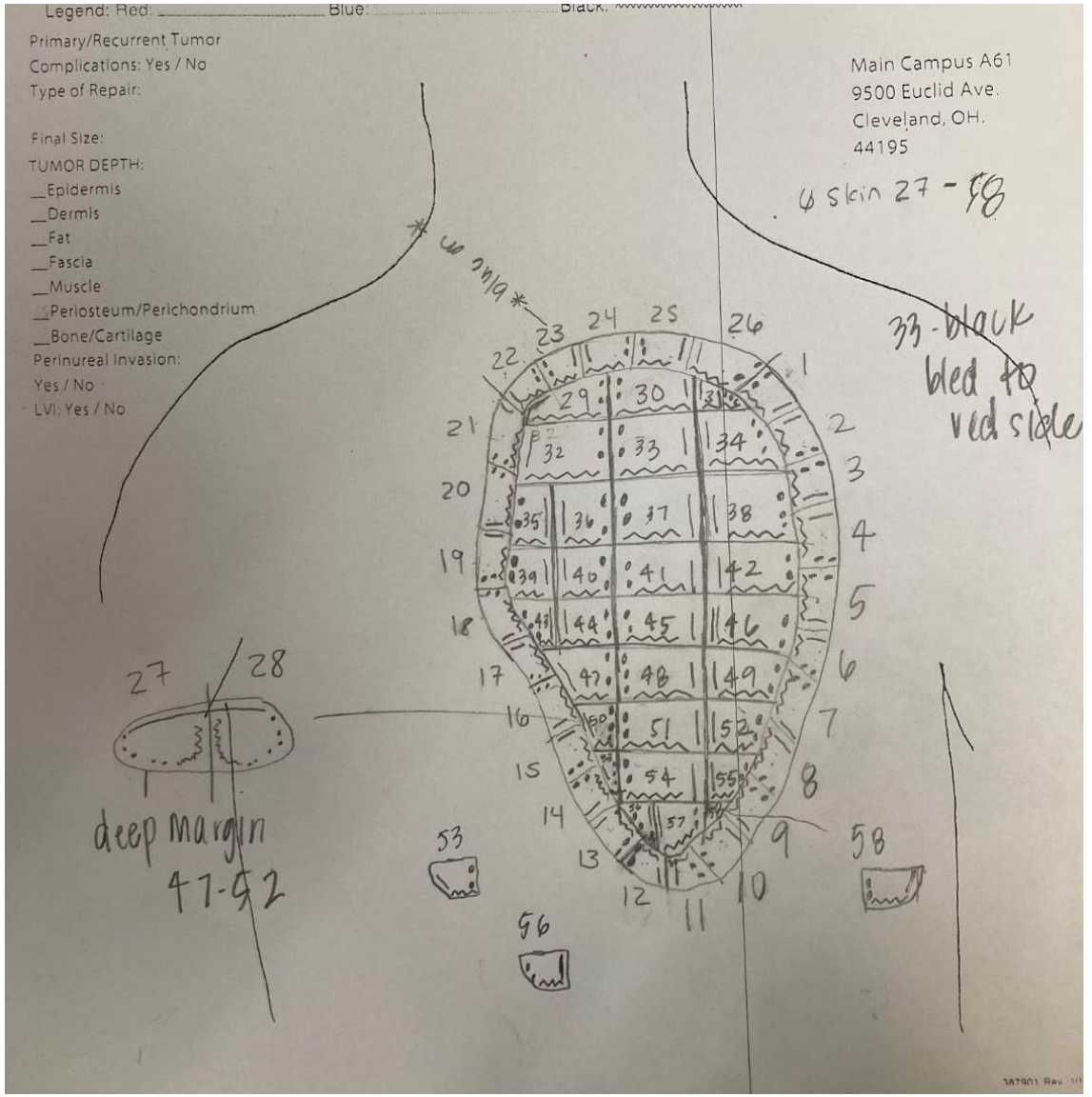


17 year old female with congenital DFSP back

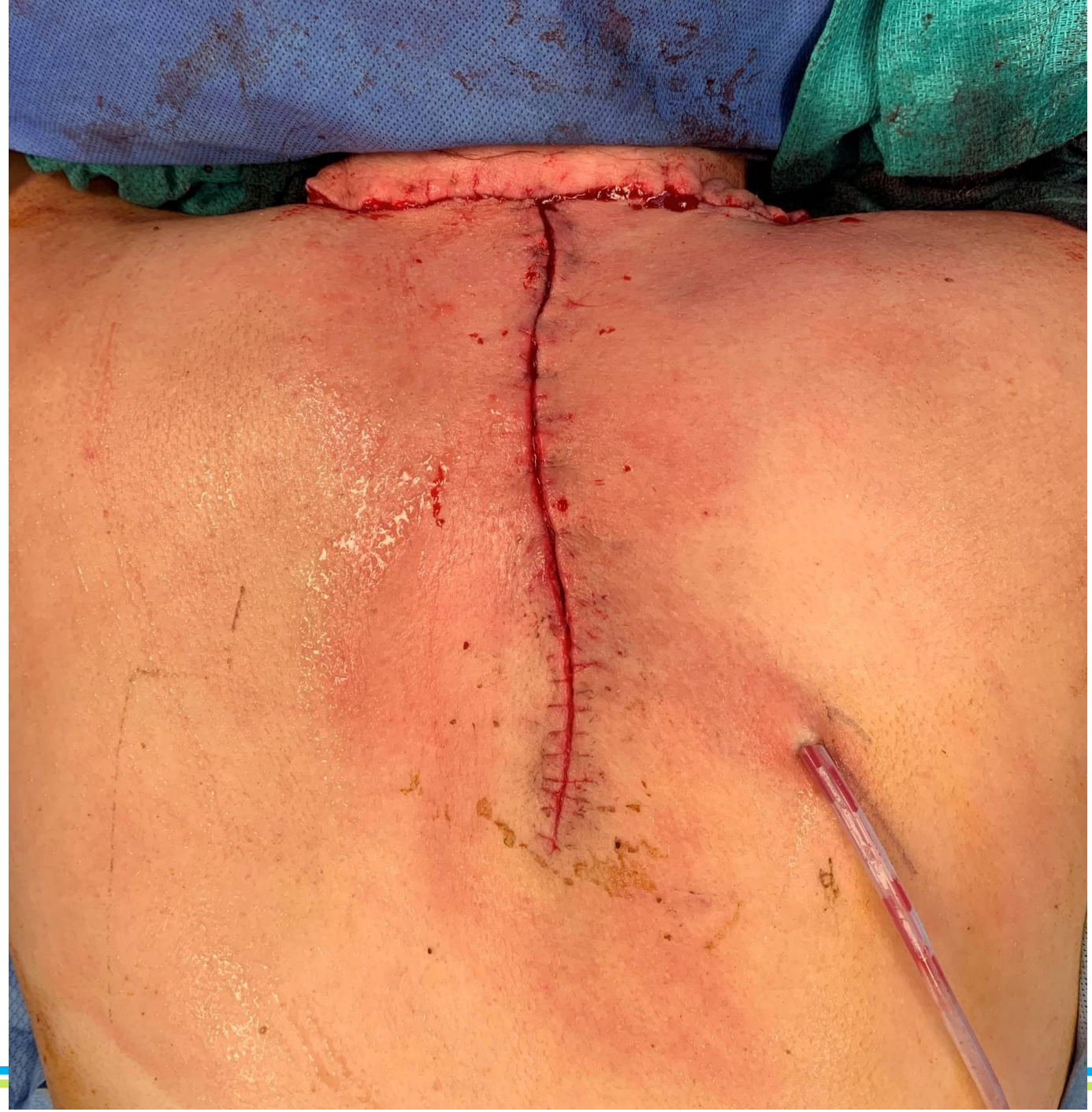


Mohs (slow) tissue read 8-25-21





A layer clear, no FS change
8-25-21



8-31-21 repair
NED March 2024

Congenital DFSP

- Rare, 70 cases in literature
- Often misdiagnosed
- Average age at diagnosis **14 yo**
- COLA1A/PDFGFb most common mutation in DFSP
- PLEKHH2-ALK gene fusion
  - Not previously reported in DFSP

Ward RE, Stultz TW, Billings SD, Vidimos AT. Mohs Micrographic Surgery for Congenital Scalp Dermatofibrosarcoma Protuberans With Novel PLEKHH2-ALK Gene Fusion. Dermatol Surg 2024; 50: 291-3.

Congenital DFSP

- **MMS treatment of choice over WLE***
  - 11/61 cases treated with **MMS** with **0% recurrence** at avg fu 4.3 years
  - 50/61 cases treated with **WLE** with **11% recurrence rate** at avg fu 1.9 yrs
  - No reports of metastatic congenital DFSP
  - Excised margins smaller with MMS vs WLE (1.7cm vs 2.8cm), avg 2 stages MMS
  - Challenges: prolonged tissue processing time, coordination with surgical subspecialists

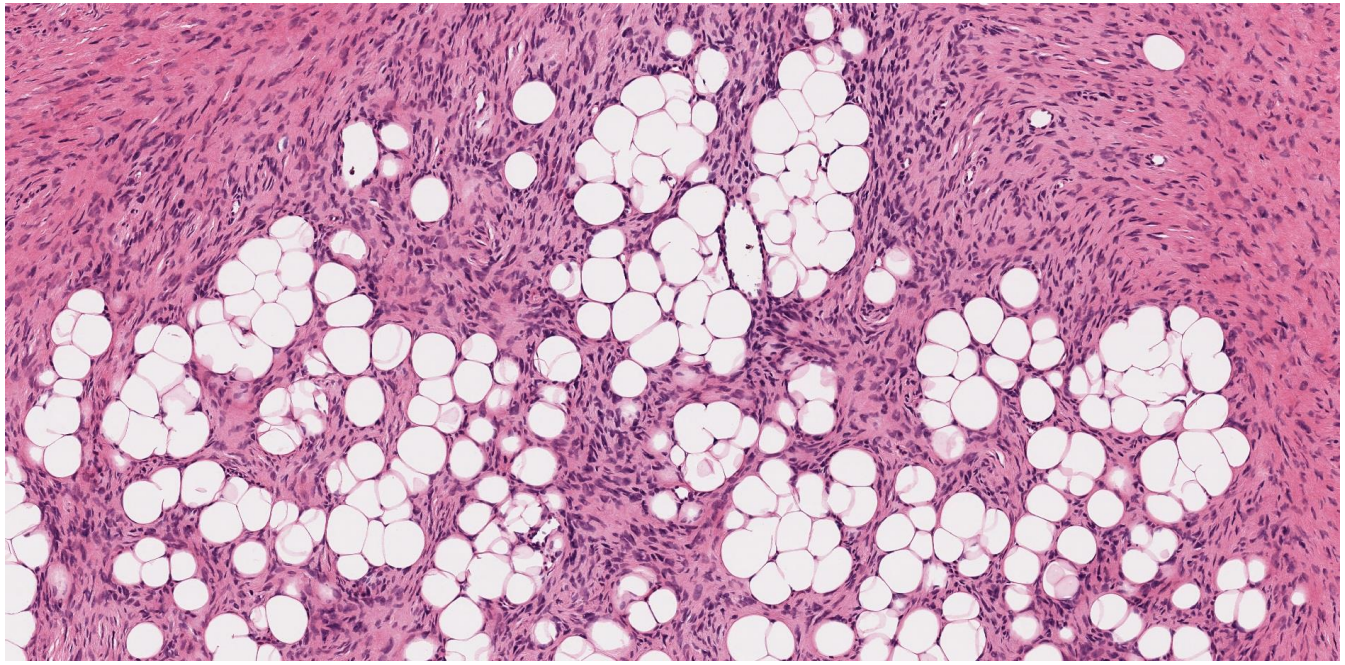
Love WE et al. Surgical management of congenital dermatofibrosarcoma protuberans, J Am Acad Dermatol 2009; 61:1014-23.

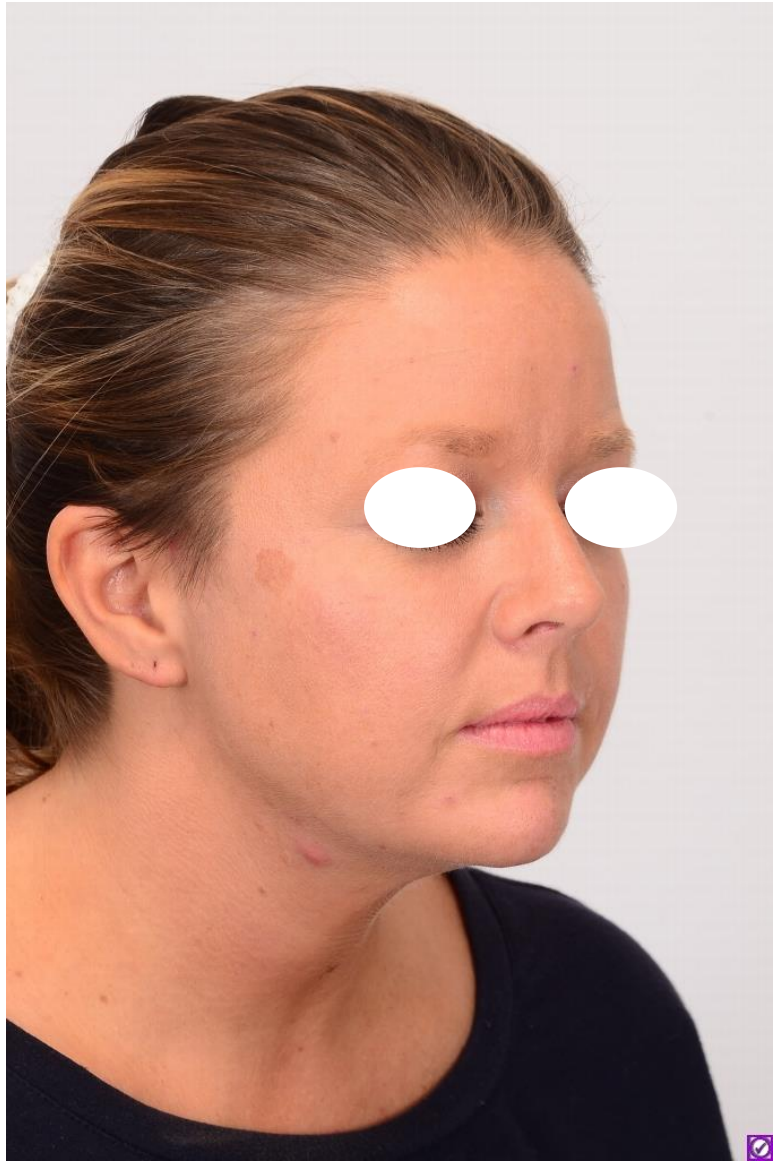
Multicentric dermatofibrosarcoma protuberans in patients with adenosine deaminase-deficient severe combined immune deficiency. Kasserwan C et al. J Allergy Clin Immunol 2012; 129: 762-9.

- 8/12 patients with ADA- SCID had DFSP, primarily T&E
- 7/8 had multicentric involvement (4-15 tumors)
- Age 2-22, avg 8.9 years old
- Most were 2-15mm round atrophic plaques, nodular in 3 patients
- 2/8 had findings of giant cell fibroblastoma, 1/8 classic storiform pattern of spindle cells, 5/8 has nonspecific pattern of CD34+ spindle cells
- FISH positive for fusion of COLA1A and PDGFB loci in 7 patients
- ADA-SCID patients should have FBSE

HISTORY - SD

- 37 yowf consult for primary tumor right preauricular skin
- Excised as a cyst by outside MD
- Otherwise healthy
- No history of trauma to this site
- Pathology= DFSP
- Facial nerve function intact

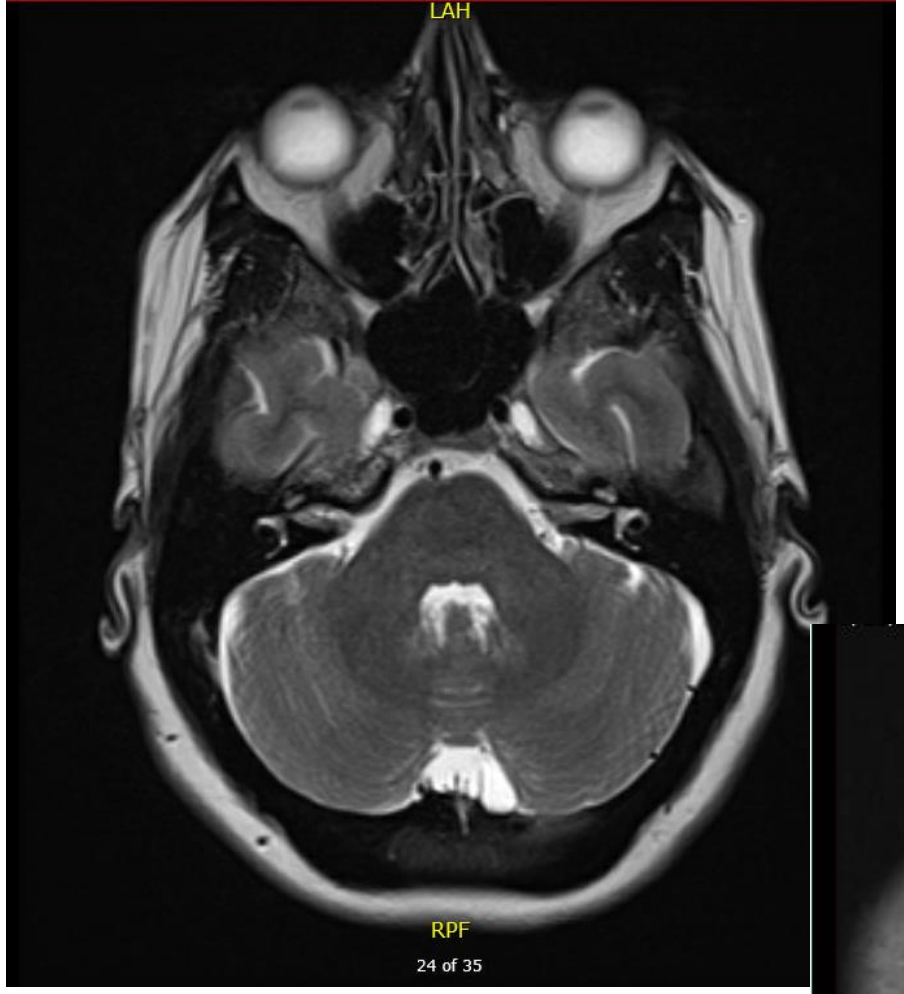


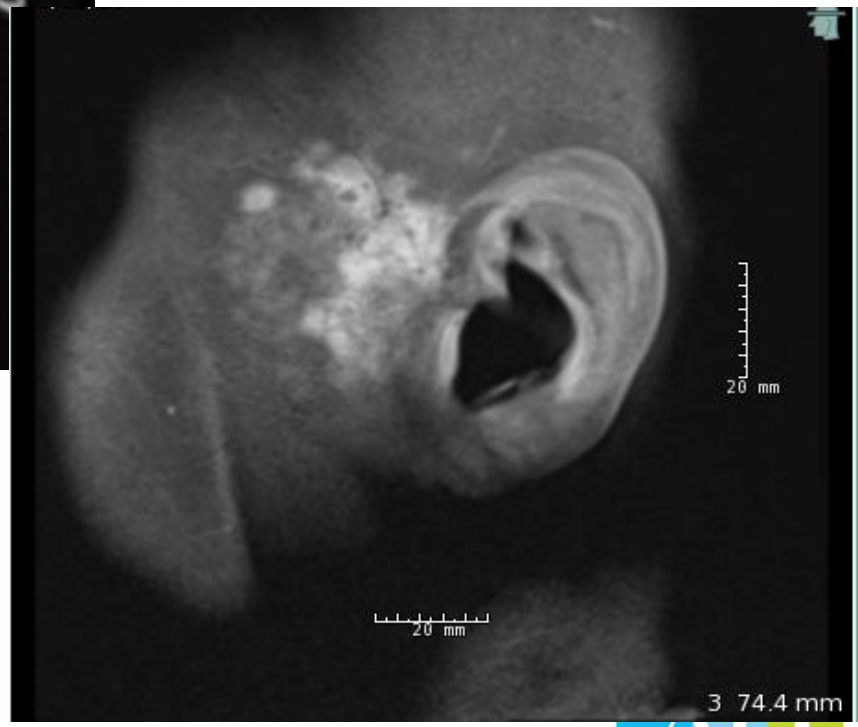


11/15/2019

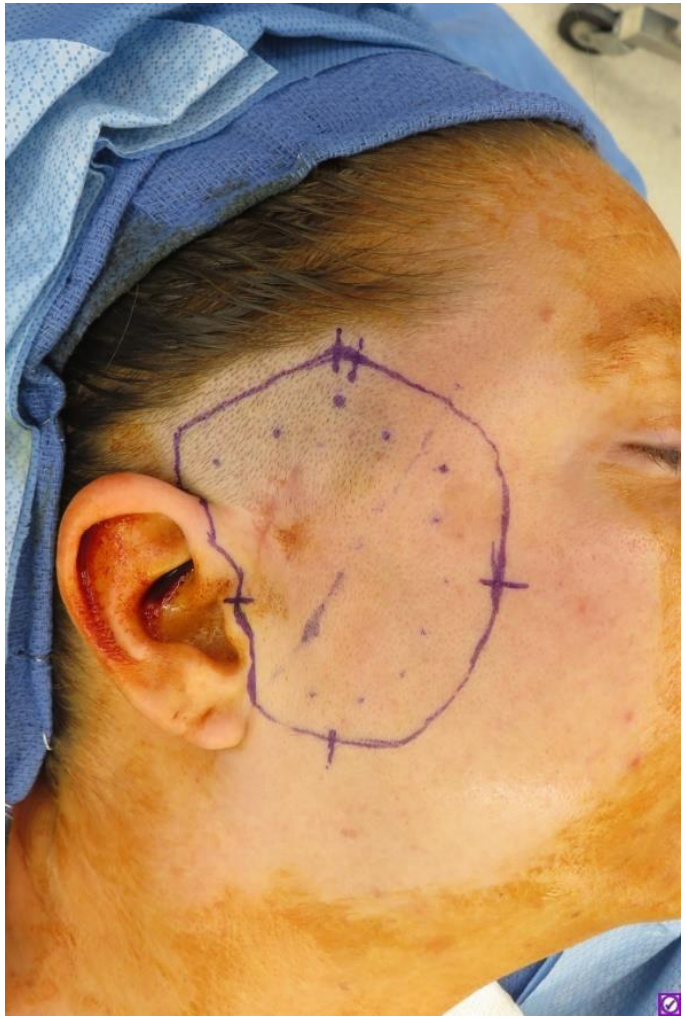
MRI

Nodular enhancing mass in the right preauricular space compatible with
the reported clinical history of dermatofibrosarcoma protuberans. While
there are no imaging findings to suggest direct invasion into the right
parotid gland, loss of the intervening fat plane as seen on a single
image as described above does not exclude this possibility.

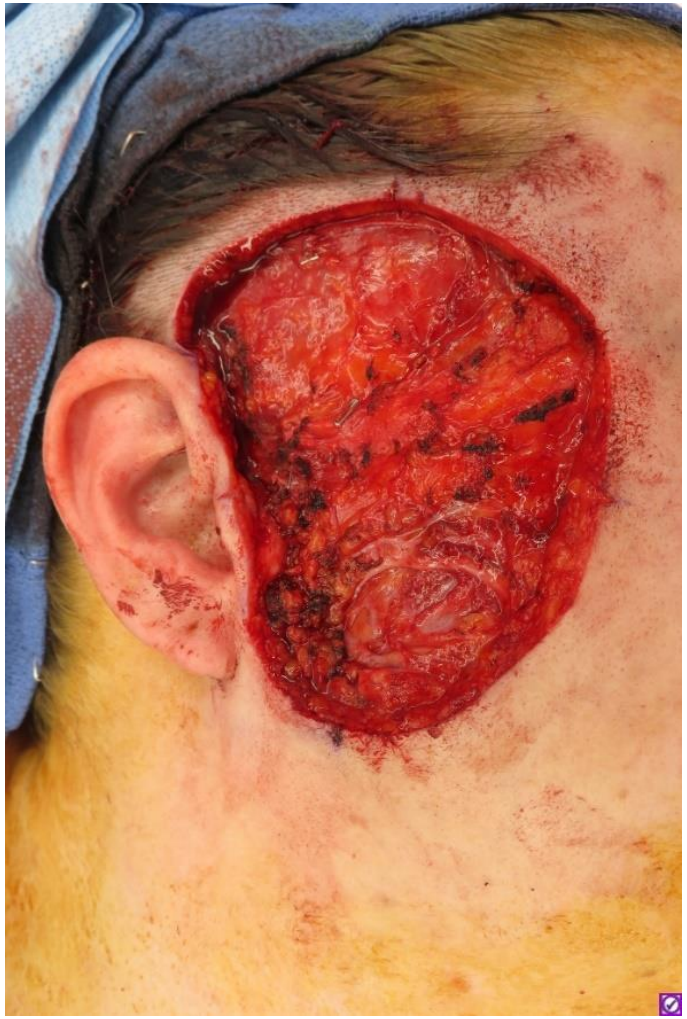




11-15-19



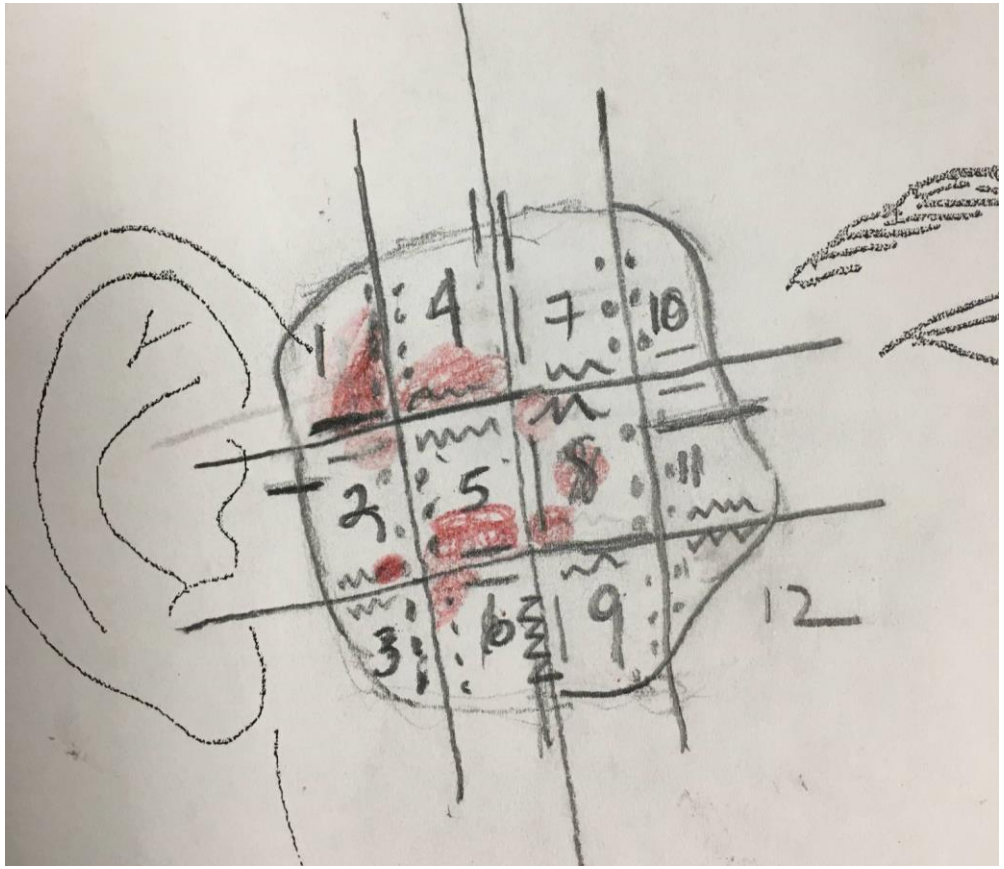
12/17/2019 Excision in main OR by facial plastic surgeon, Mohs tissue read

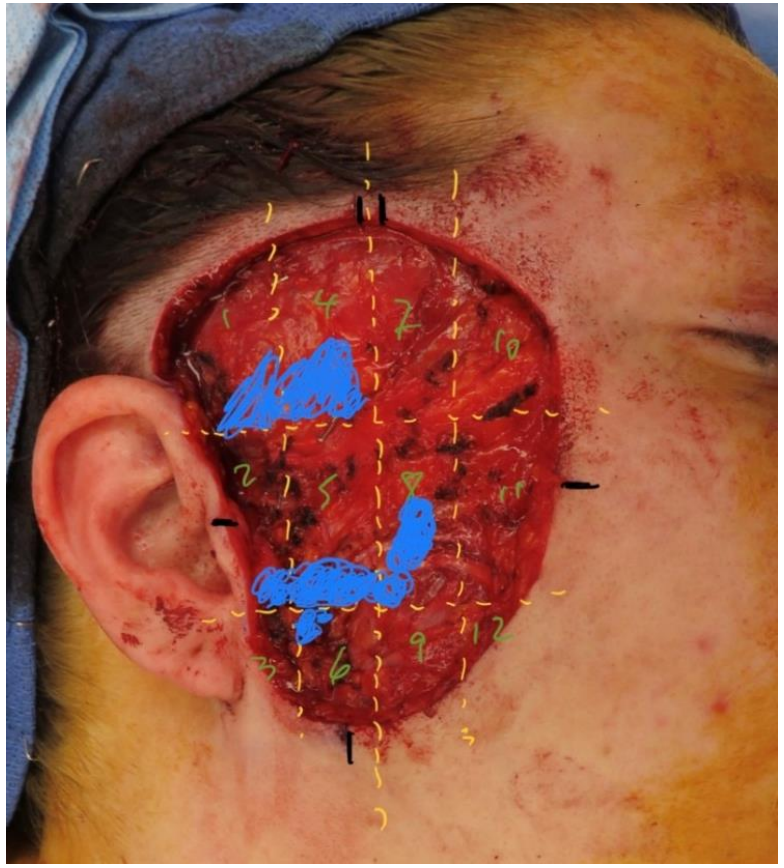


12/17/2019, after A layer

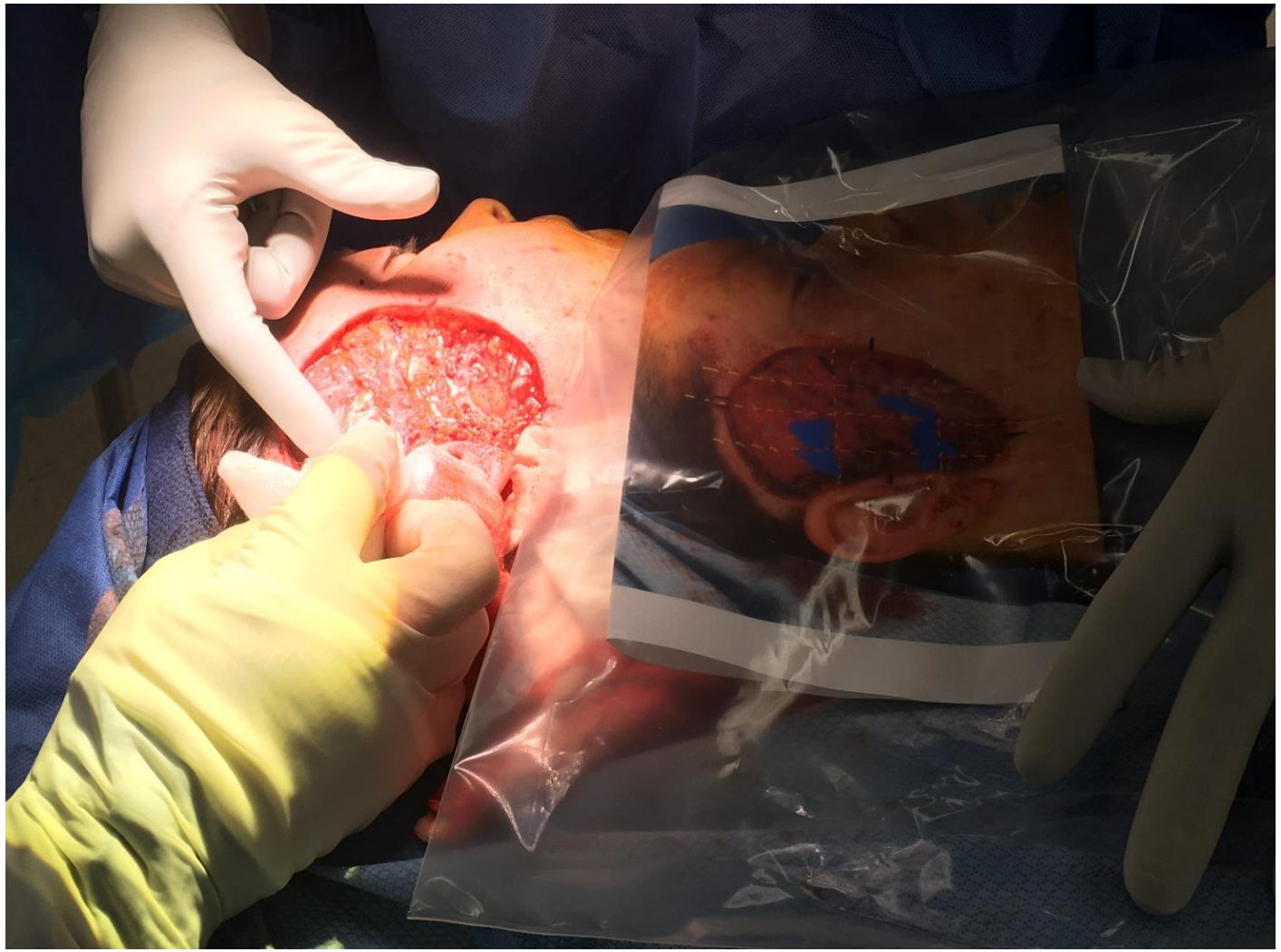
History - SD

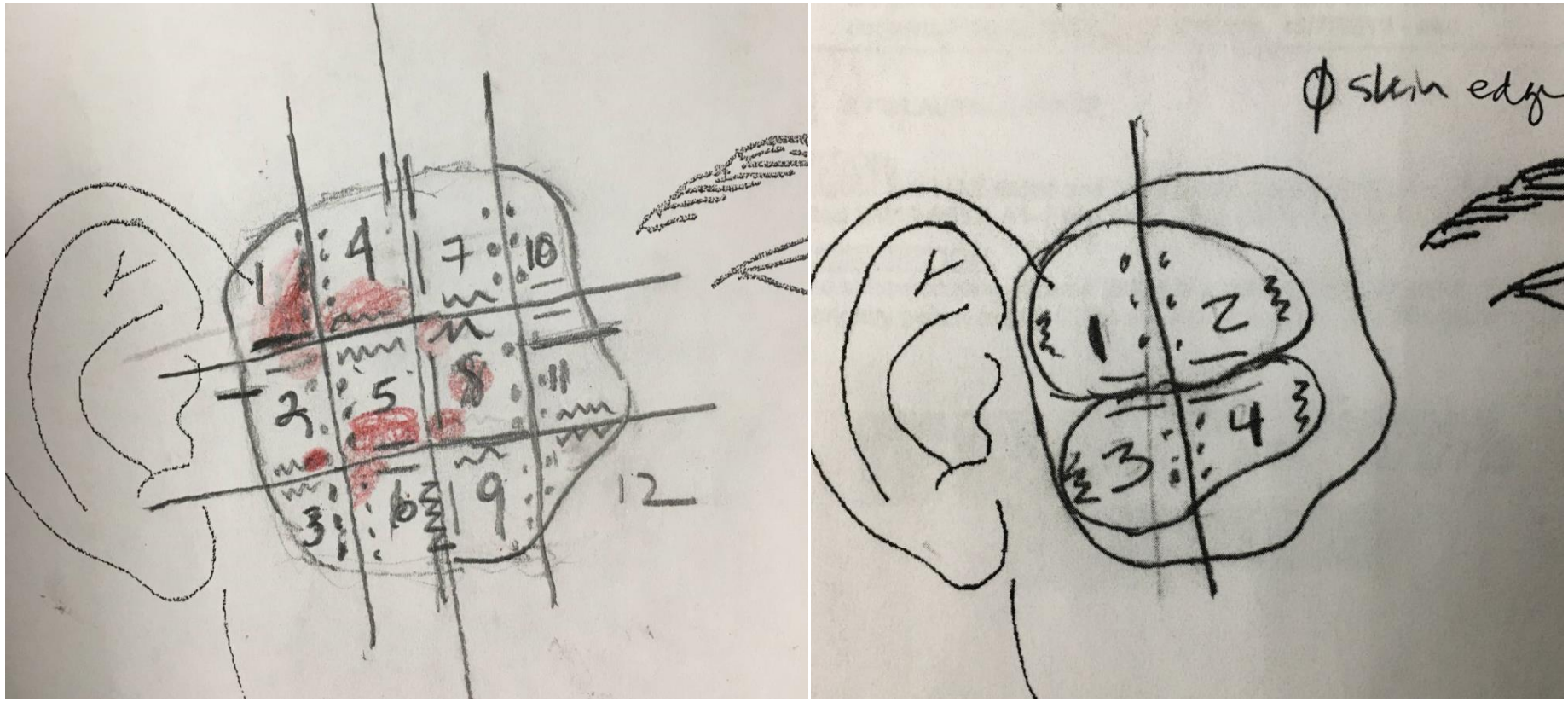
- Patient voiced desire preoperatively to preserve facial nerve function as much as possible
- A layer positive focally around facial nerve branches, temporal branch removed
- B layer taken to preserve rest of facial nerve, superficial parotidectomy performed



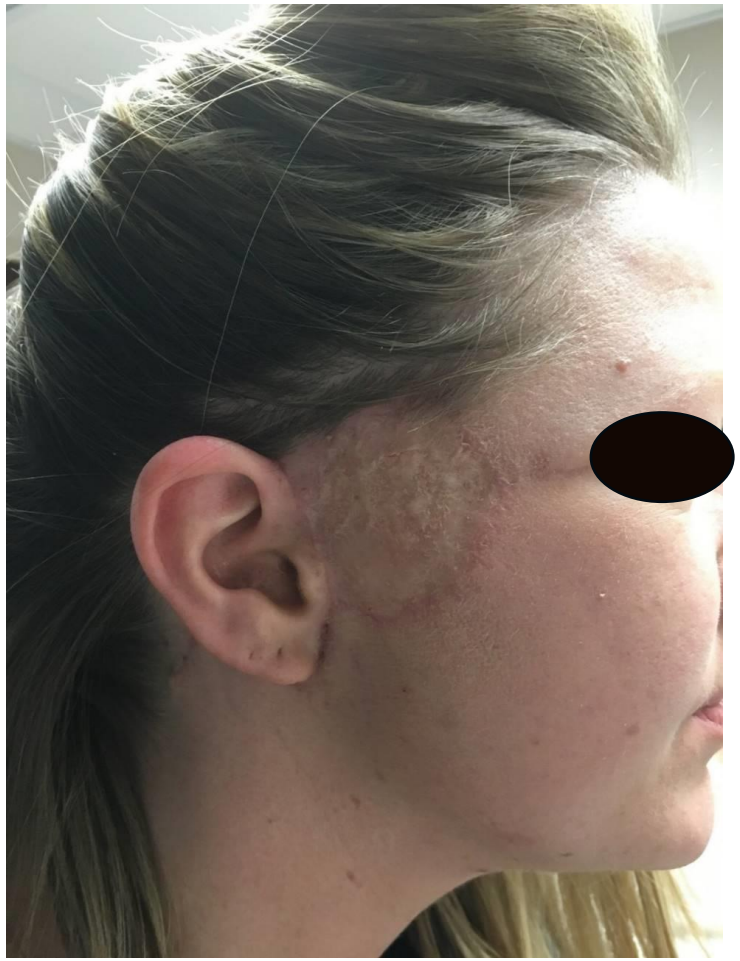


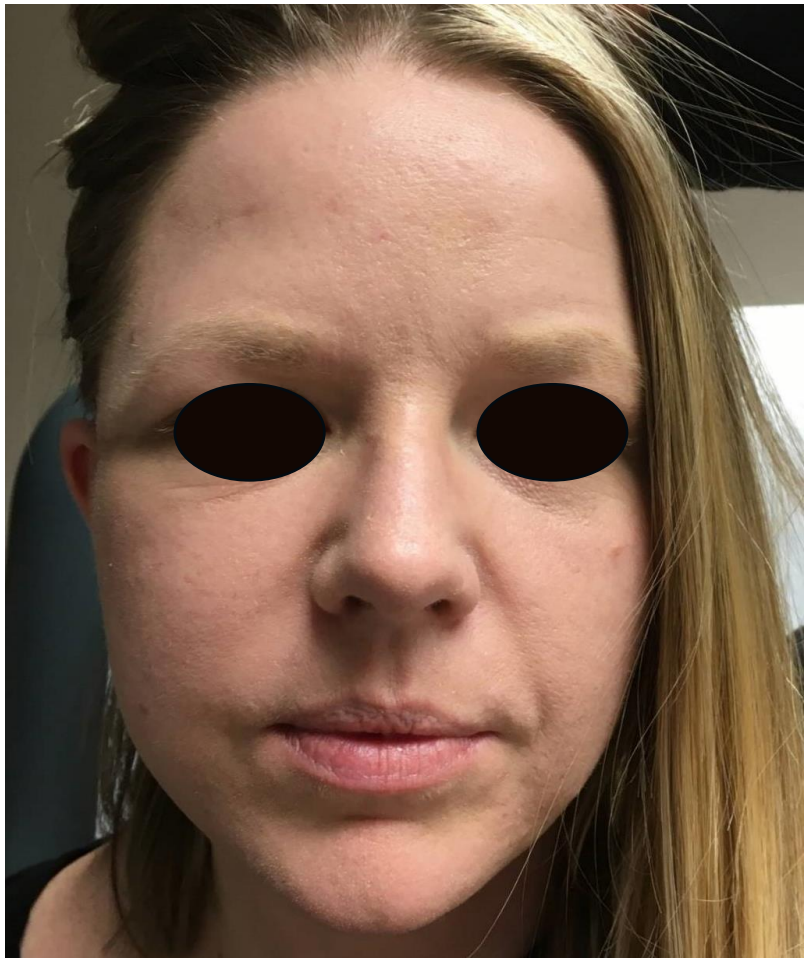
A layer map
12-17-19





-B layer taken to spare facial nerve branches
-Nonmarginal tissue sent for permanent sections – NO DFSP-FS changes noted

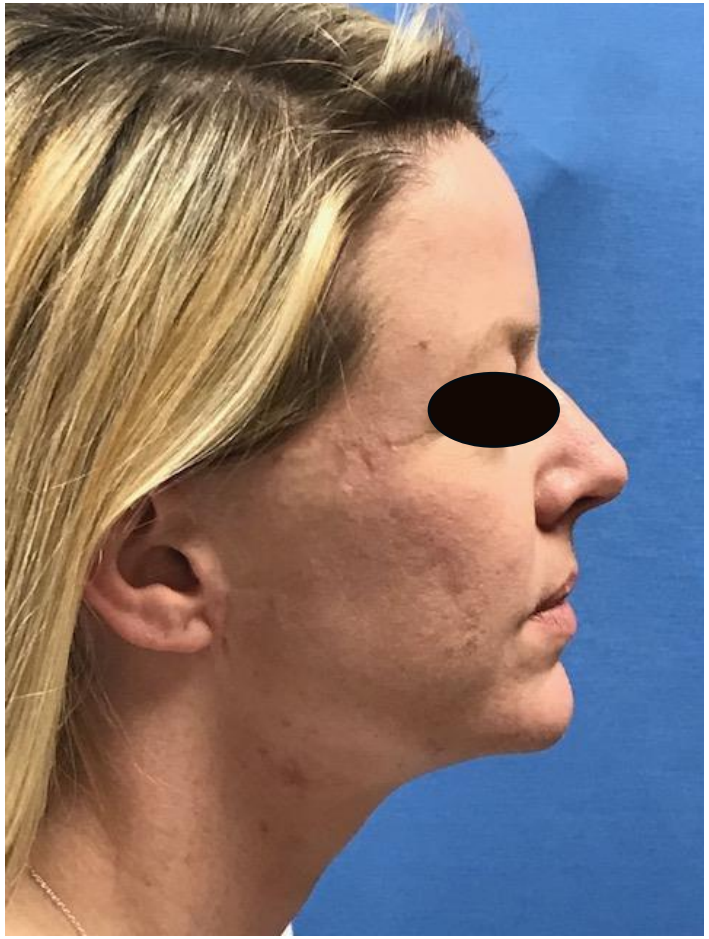


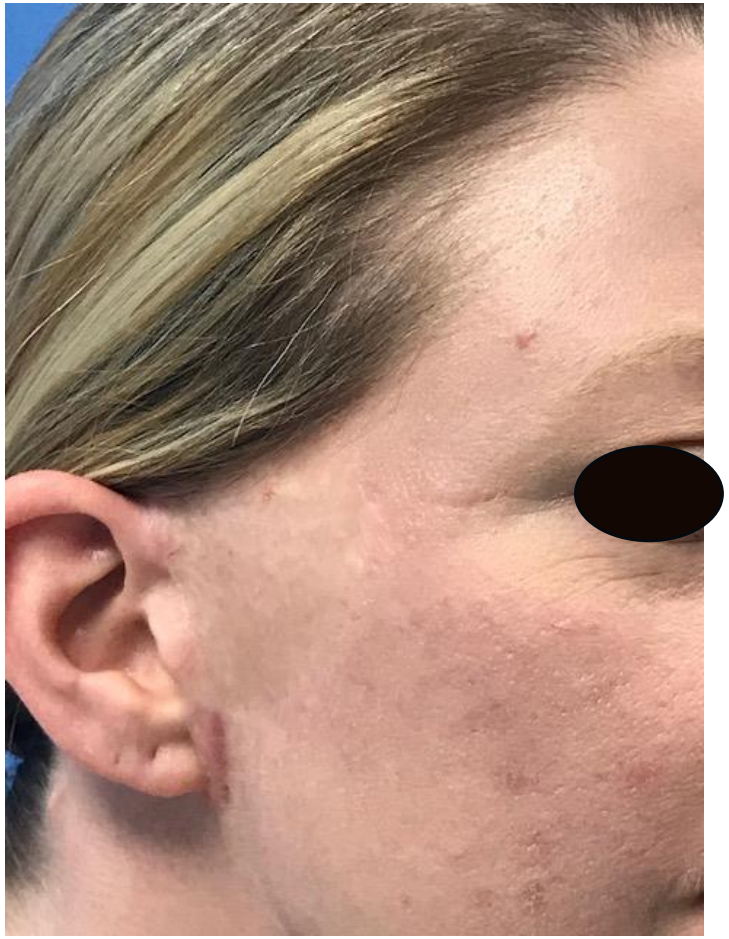


s/p cervicofacial flap and ALT free flap and STSG and frontal nerve jump grafting

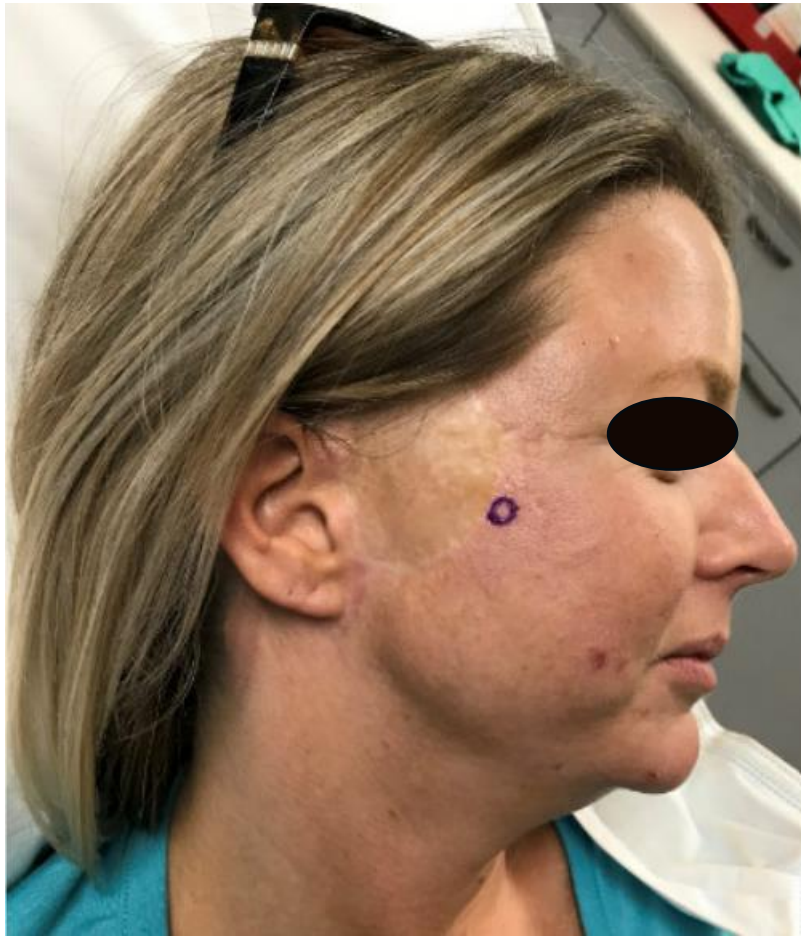
History - SD

- In light of young age of patient, imatinib 400mg/d was prescribed by medical oncologist for 12 months
- Stopped after 6 months due to elevated LFTs
- MRI and PE 2-1-21 and 5-16-22 NED
- Will follow with q 6 month MRI and PE





2-1-21



5-16-22
Bx = scar
MRI NED 29 months postop

Follow up
DFSP

- Follow up exams every 4-6 months for 3 years then every 6-12 months
- Monthly self exams
- Most recurrences occur in first 3 years post op, and 30% of recurrences are seen after 5 years
- MRI with contrast may be helpful to detect recurrences in high risk lesions

Elevated risk of subsequent primary malignancies in patients with dermatofibrosarcoma protuberans: An updated retrospective cohort analysis of Surveillance, Epidemiology, and End Results (SEER) Program.

Joshi TP, Shimizu I. J Am Acad Dermatol 2024; e1-2.

- 7791 DFSP from SEER database (2000-2020)
- 7.78% of DFSP patients developed subsequent primary malignancies (SPM) (cumulative SIR of 1.46 and EAR of 30.15 per 10,000 person years)
- Increased risk of melanoma, and cancer of breast, nonepithelial skin and soft tissue, vulva, thyroid, brain, and kidney/renal pelvis
- Latency analysis revealed persistently elevated risk of many SPMS even after 10 years after initial DFSP diagnosis
- Certain SPMs may be due to shared molecular mechanisms (over expression of PDGF in several malignancies incl breast, GBM, melanoma, and thyroid); treatment effects (eg radiation therapy) and shared environmental exposures may also be potential culprits
- Emphasizes need for annual dermatologist and primary care physician follow up

THANK YOU!

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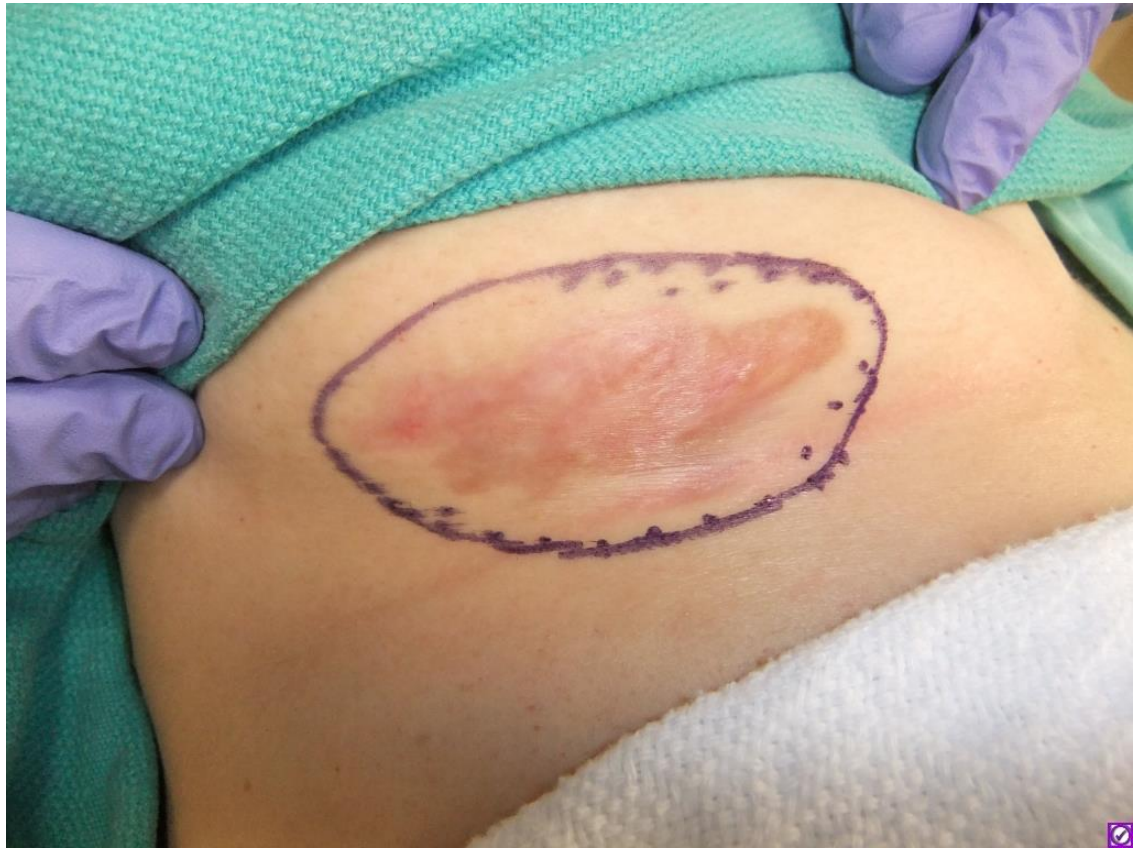
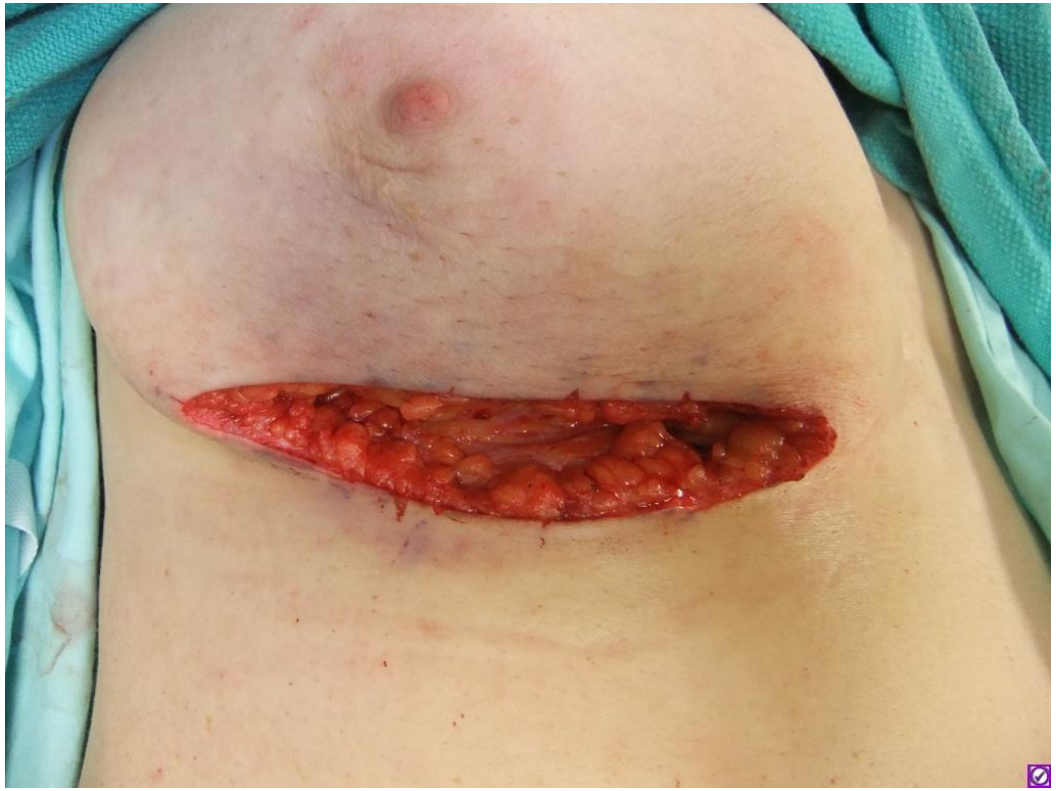
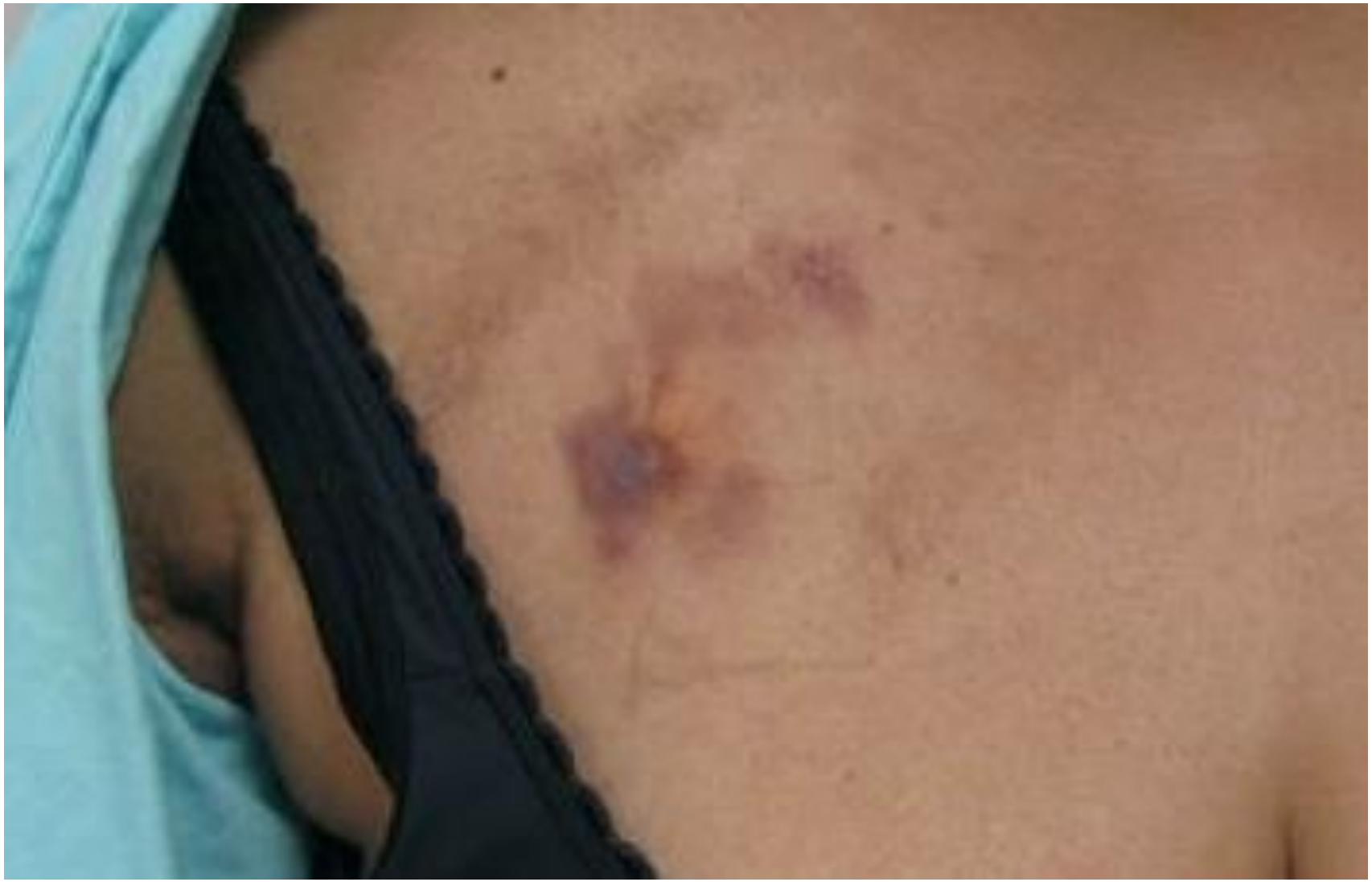
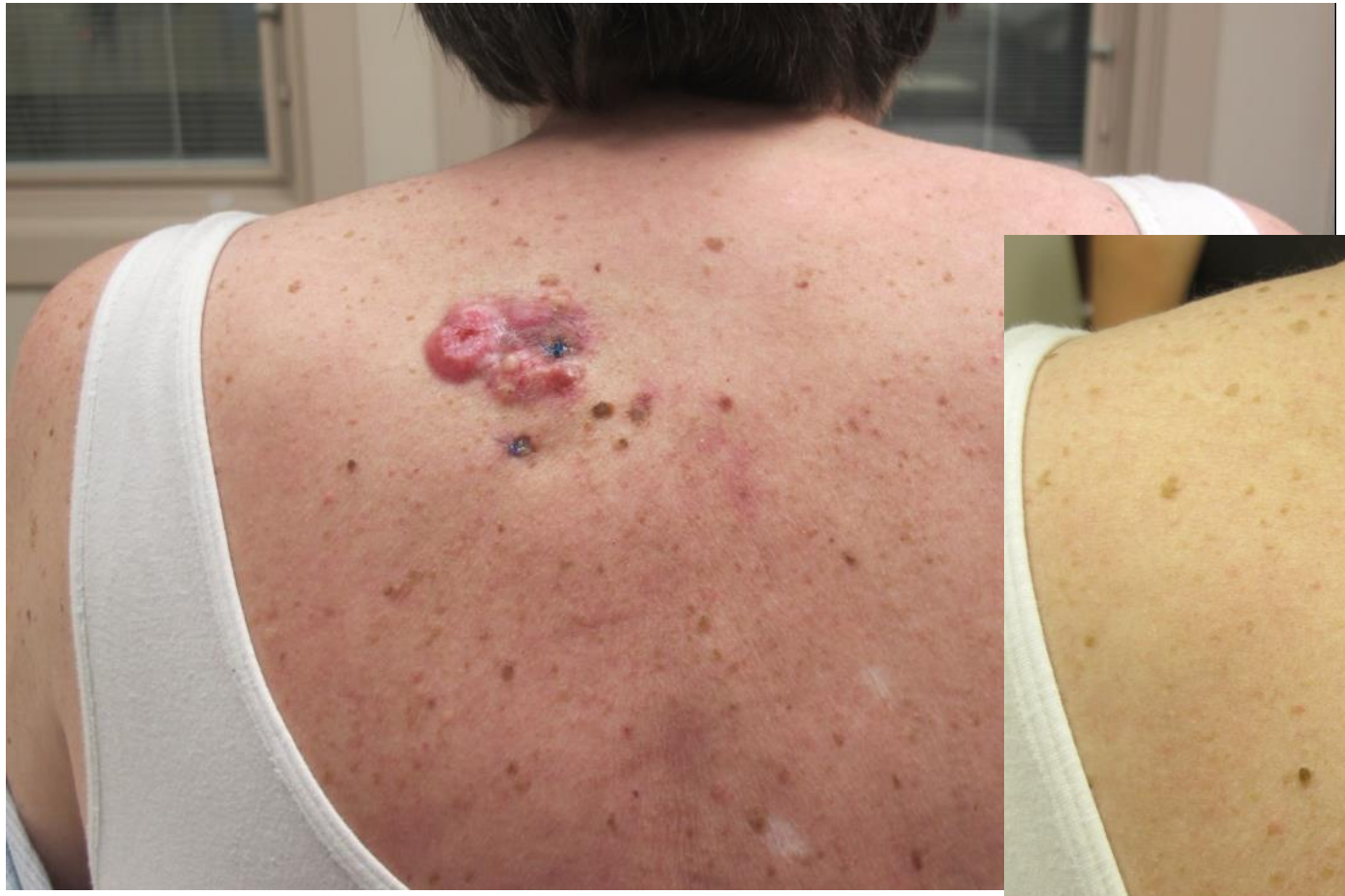
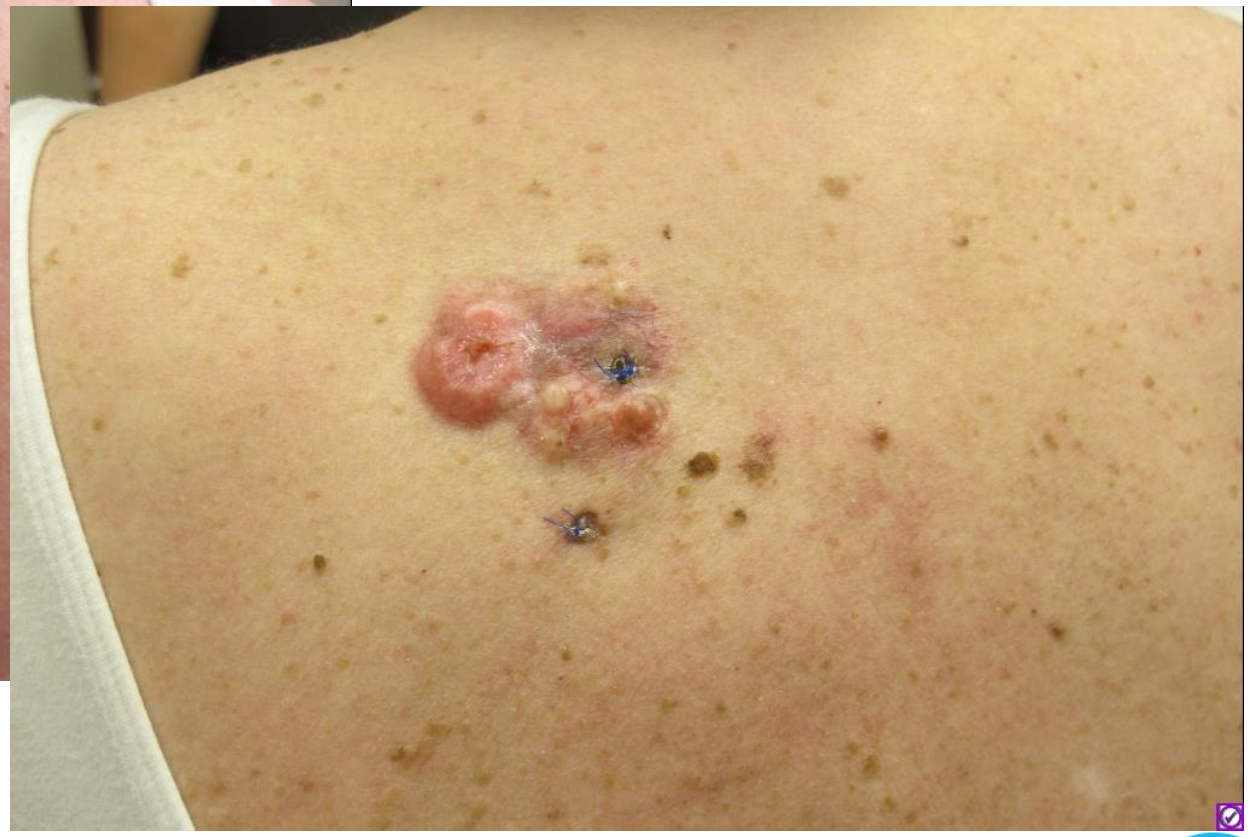
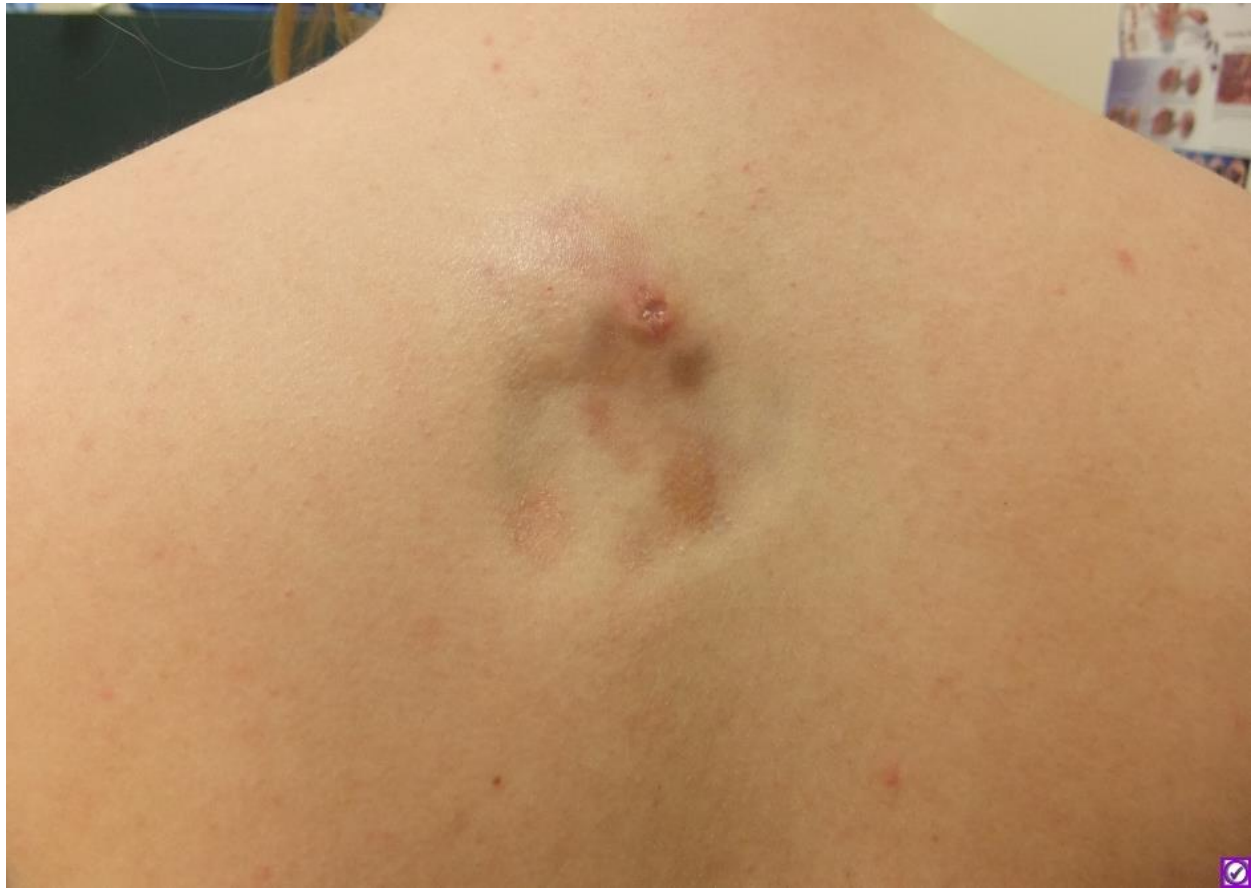


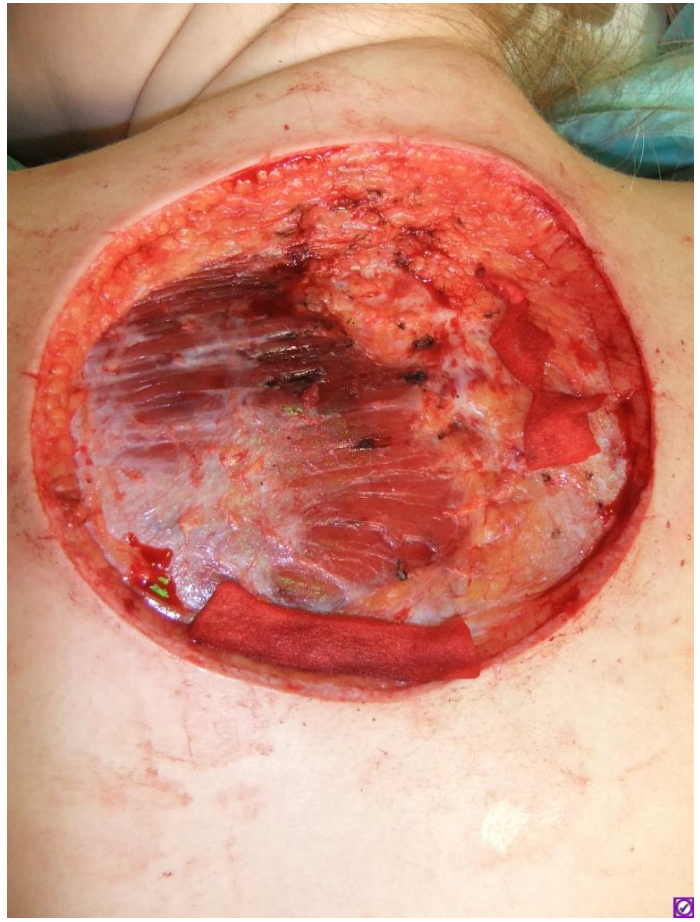


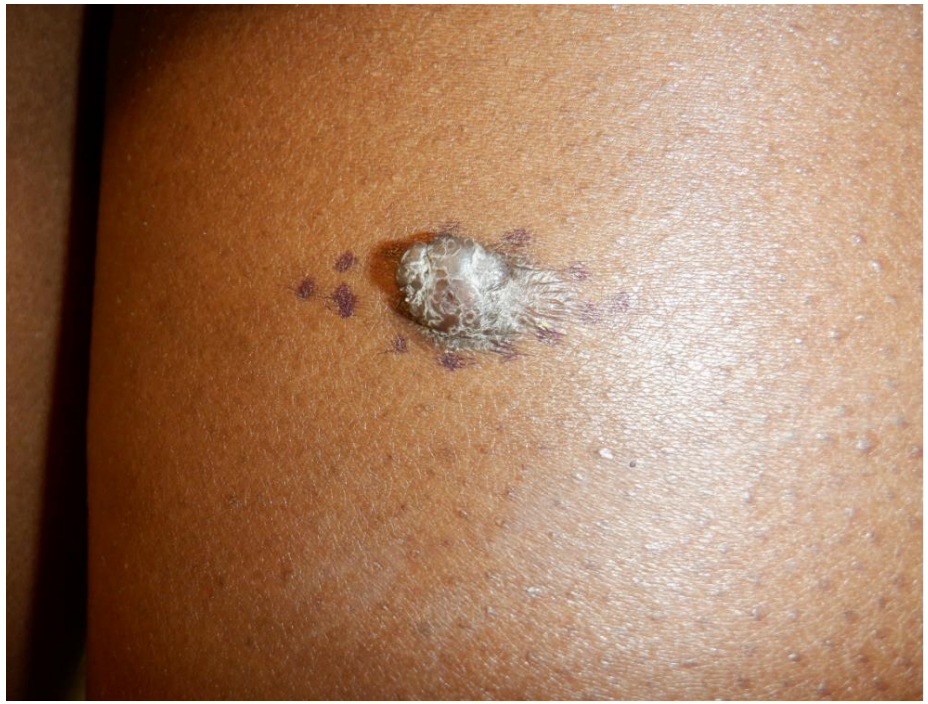








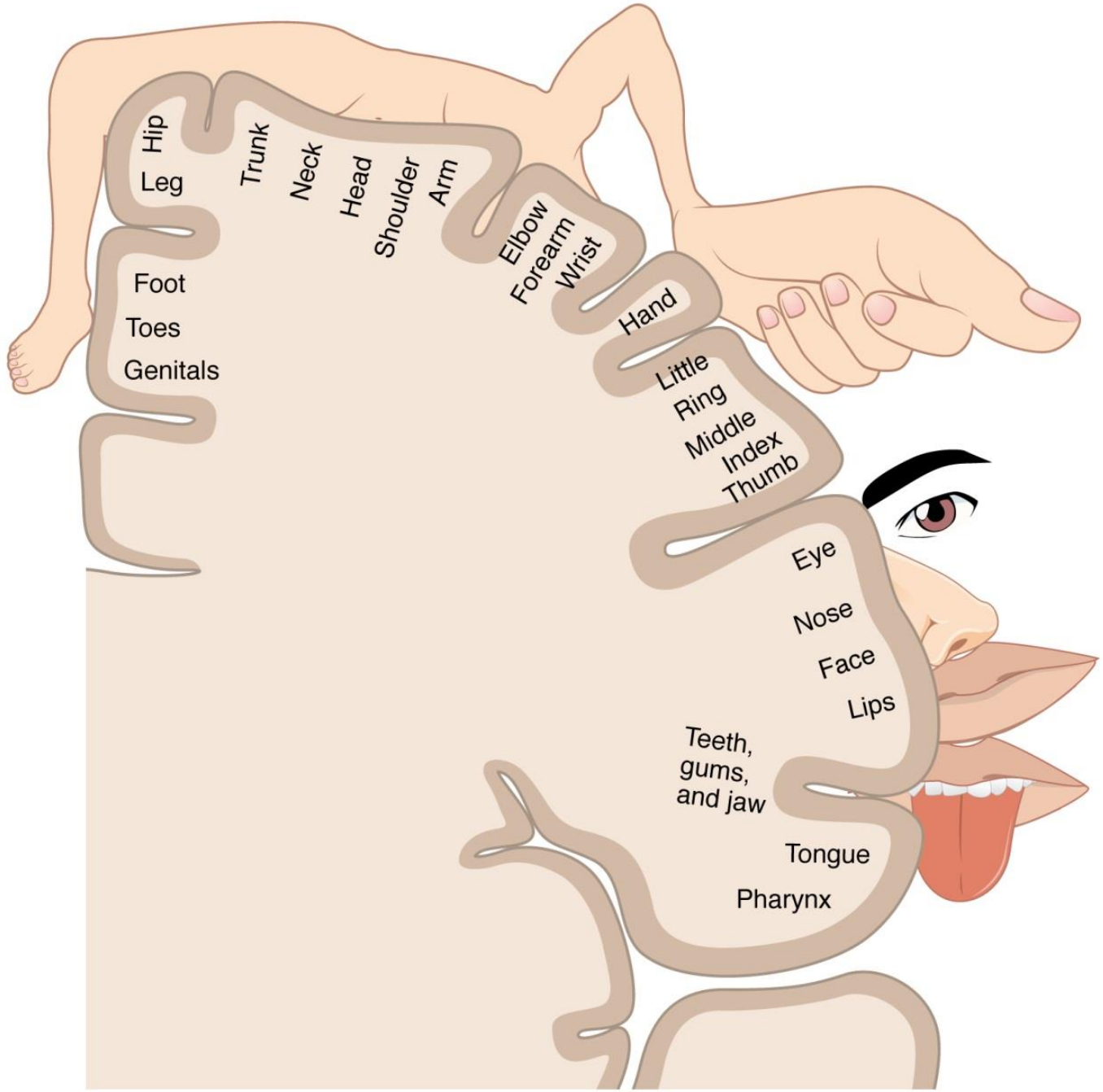


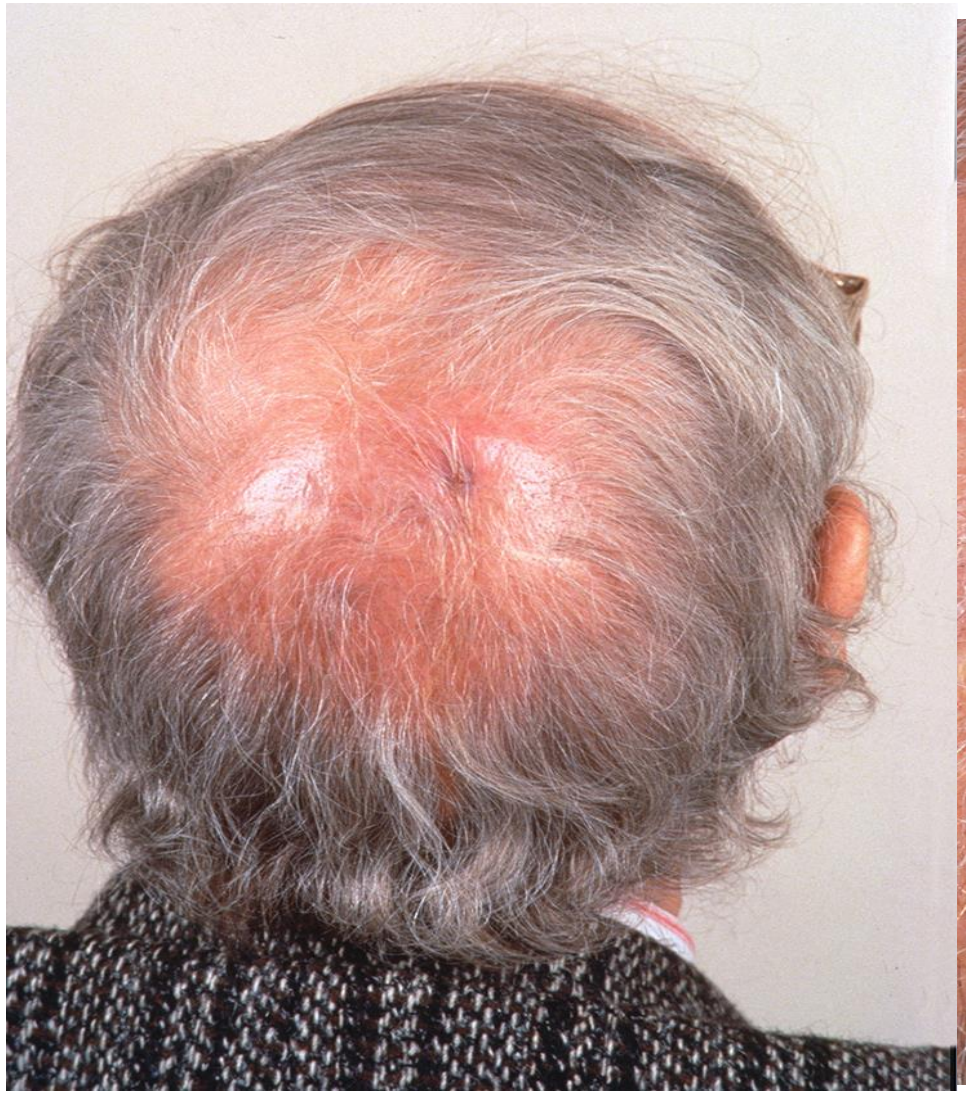


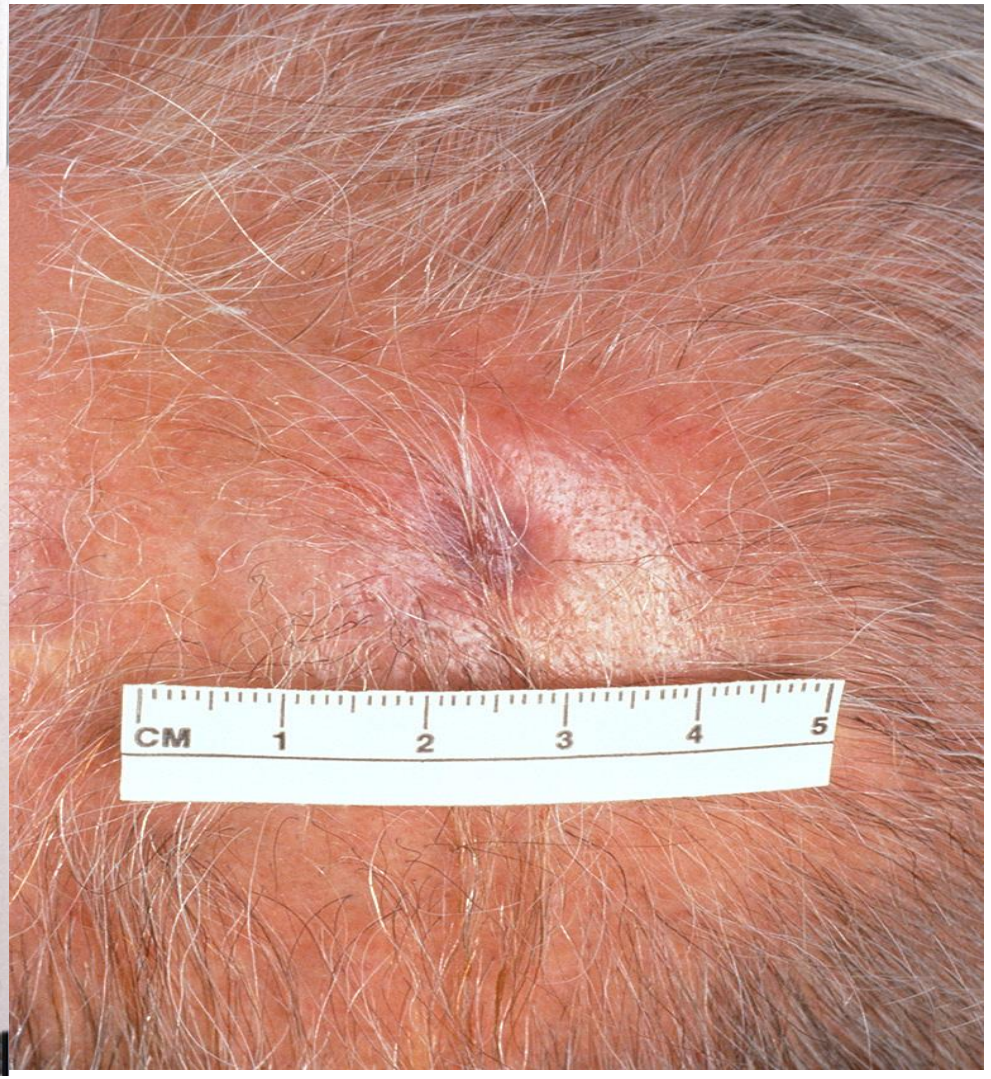
A No Brainer?!

HISTORY

- 64 yowm referred by neurology for biopsy of 8mm scalp erosion of 2 months duration (1992, paper charts)
- No prior history of skin cancer
- PMH - CHF, MI, seizures after MVA head trauma
- Meds - Dilantin, Lanoxin, Isordil, Zantac, Lasix
- Shave biopsy in medical dermatology clinic - clear yellow fluid
- Resident: “I think I see brain”


Hip
Leg
Trunk
Neck
Head
Shoulder
Arm
Elbow
Forearm
Wrist
Hand
Foot
Toes
Genitals
Little
Ring
Middle
Index
Thumb
Eye
Nose
Face
Lips
Teeth, gums, and jaw
Tongue
Pharynx




CM
1
2
3
4
5

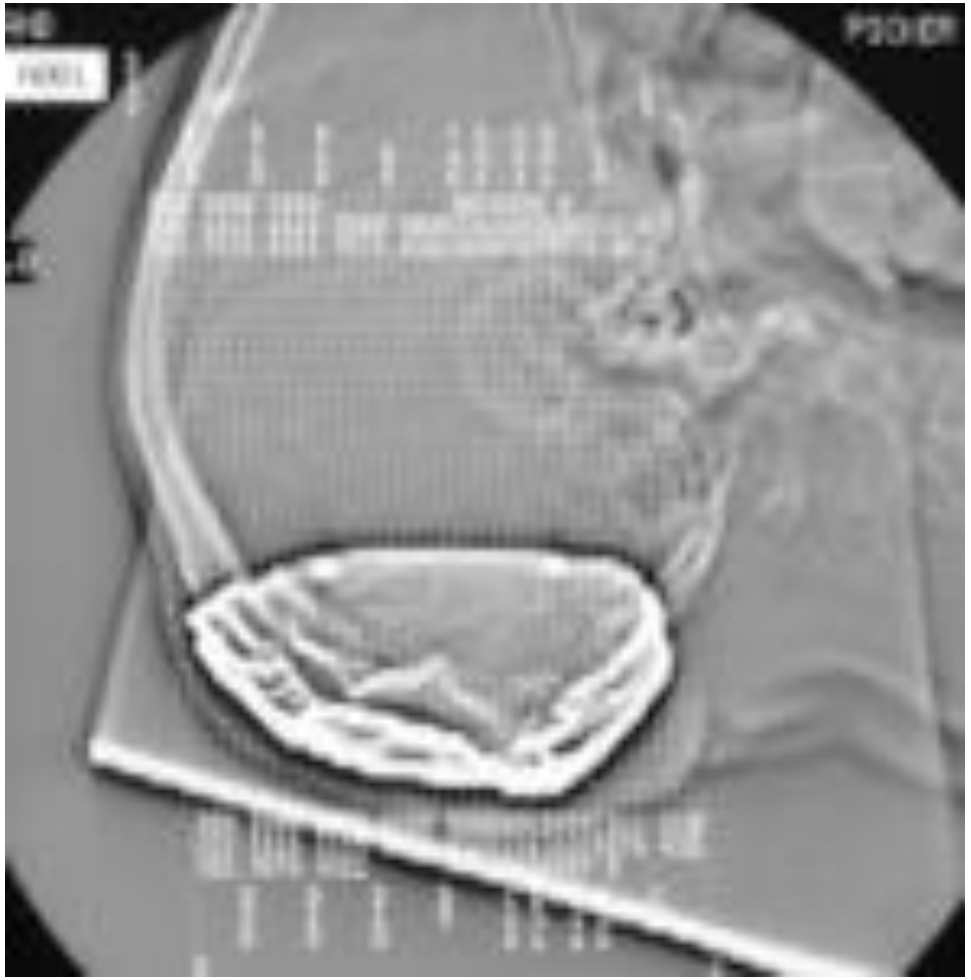
HISTORY

- Patient had tantalum metal plate placed to cover bony defect on vertex 43 years prior after MVA
- Patient was hit over head by mugger 2 months prior to appointment
- Now what?!

RESOLUTION

- Call neurosurgery!!!
- CT scan

TANTALUM CRANIAL RECONSTRUCTION PLATE



CT scout film

HISTORY

- Dislodged tantalum plate with broken screws
- Surgically removed, Staph/Strep infection
- IV antibiotics
- Waited one year, wore helmet
- Replaced plate

Cranioplasty

- Performed following head trauma to correct cosmetic defect or restore craniocerebral protection
- Materials: metals, plastics, bone (coconut shells, sea shells, tree bark, animal horns)

Cranioplasty

Complications

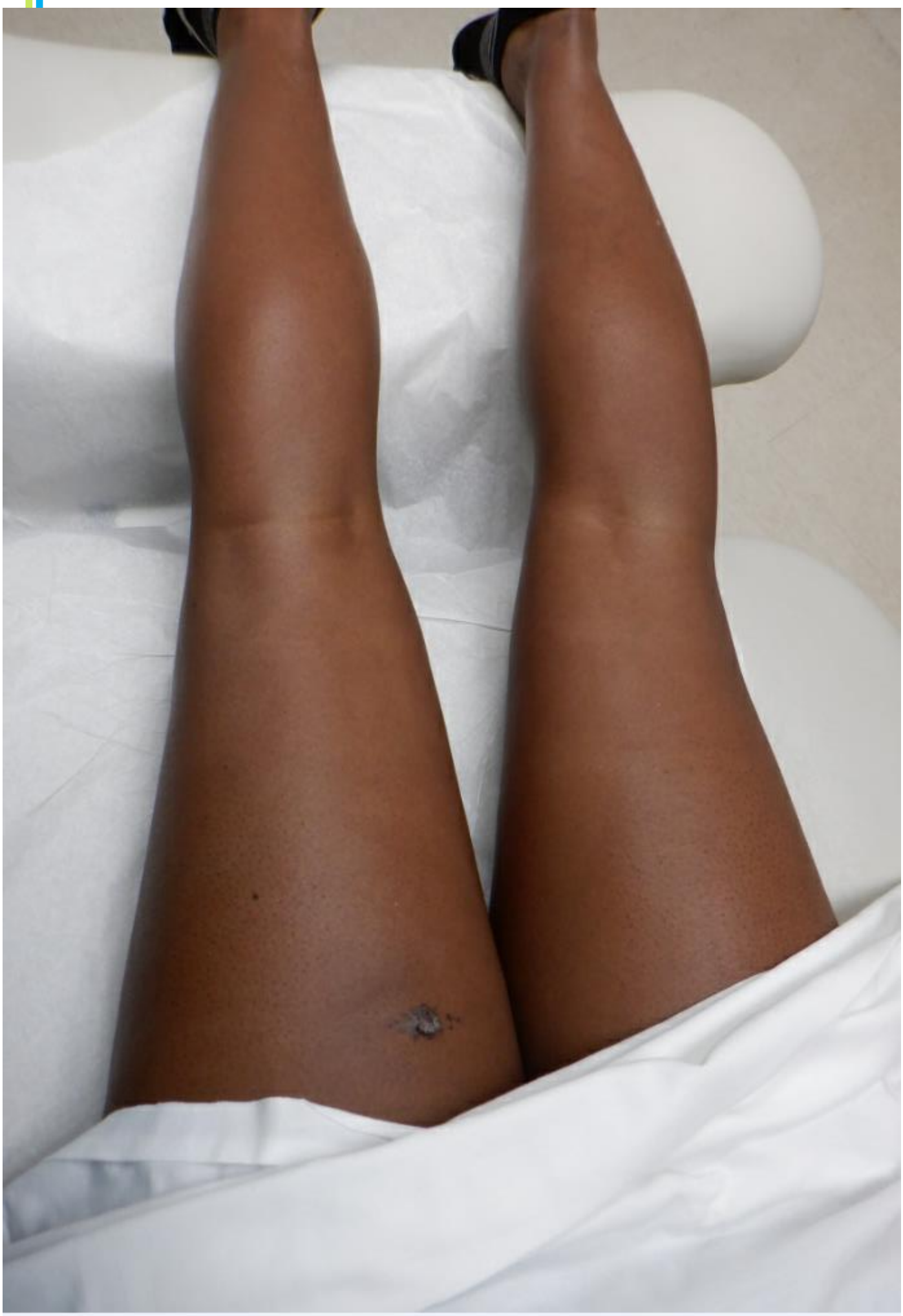
- **Infection**
- Plate loss
- Fluid accumulation
- CSF leak
- Hematoma
- **Plate fracture or dislodgement**
- Unstable (mobile) plate

Efficacy of Mohs Micrographic Surgery for the Treatment of Dermatofibrosarcoma Protuberans

Systematic Review

Majid Foroozan, MD; Jean-François Sei, MD; Mona Amini, MD; Alain Beauchet, MD; Philippe Saiag, MD, PhD

- Review from 1995-2011
- 23 nonrandomized trials
- Recurrence of DFSP after MMS 1.11%
- After WLE 6.32%
- Mean time to recurrence was 68 months
  - Arch Dermatol 2012; 148: 1055-63.



SEDC: The Cleveland Clinic Experience

- Retrospective chart review utilizing pathology and Mohs surgery logs to identify patients with a diagnosis of “squamoid eccrine ductal carcinoma” from 2001 – 2021
- Purpose of the study was to add to the existing literature by describing presentation, treatment, and associated outcomes of SEDC managed at the Cleveland Clinic
- In total, 17 patients were identified, however, 3 were excluded as treatment was either performed at an outside institution, or the patient refused treatment due to rapidly declining health (unrelated to SEDC)

Congenital DFSP

- Rare, 70 cases in literature
- Often misdiagnosed
- COLA1A/PDFGFb most common mutation in DFSP
- PLEKHH2-ALK gene fusion
  - Not previously reported in DFSP
  - Details: The fusion product is between **PLEKHH2 exon 6** (NM_172069.3) **and ALK exon 20** (NM_004304). **PLEKHH2** is a novel podocyte protein (PMID:22832517) that has broad expression in a variety of tissues including **lung, endometrium and skin** (www.ncbi.nlm.nih.gov/gene/130271).
  - Although PLEKHH2 is a fairly novel partner (one case report in lung adenocarcinoma, PMID:32893122), **ALK fusions** involving other partners have been described in a variety of cutaneous malignancies as well as other neoplasms (**anaplastic large cell lymphoma, Merkel cell carcinoma, melanoma, spitzoid tumors, epithelioid fibrous histiocytoma, and basal cell carcinoma**)

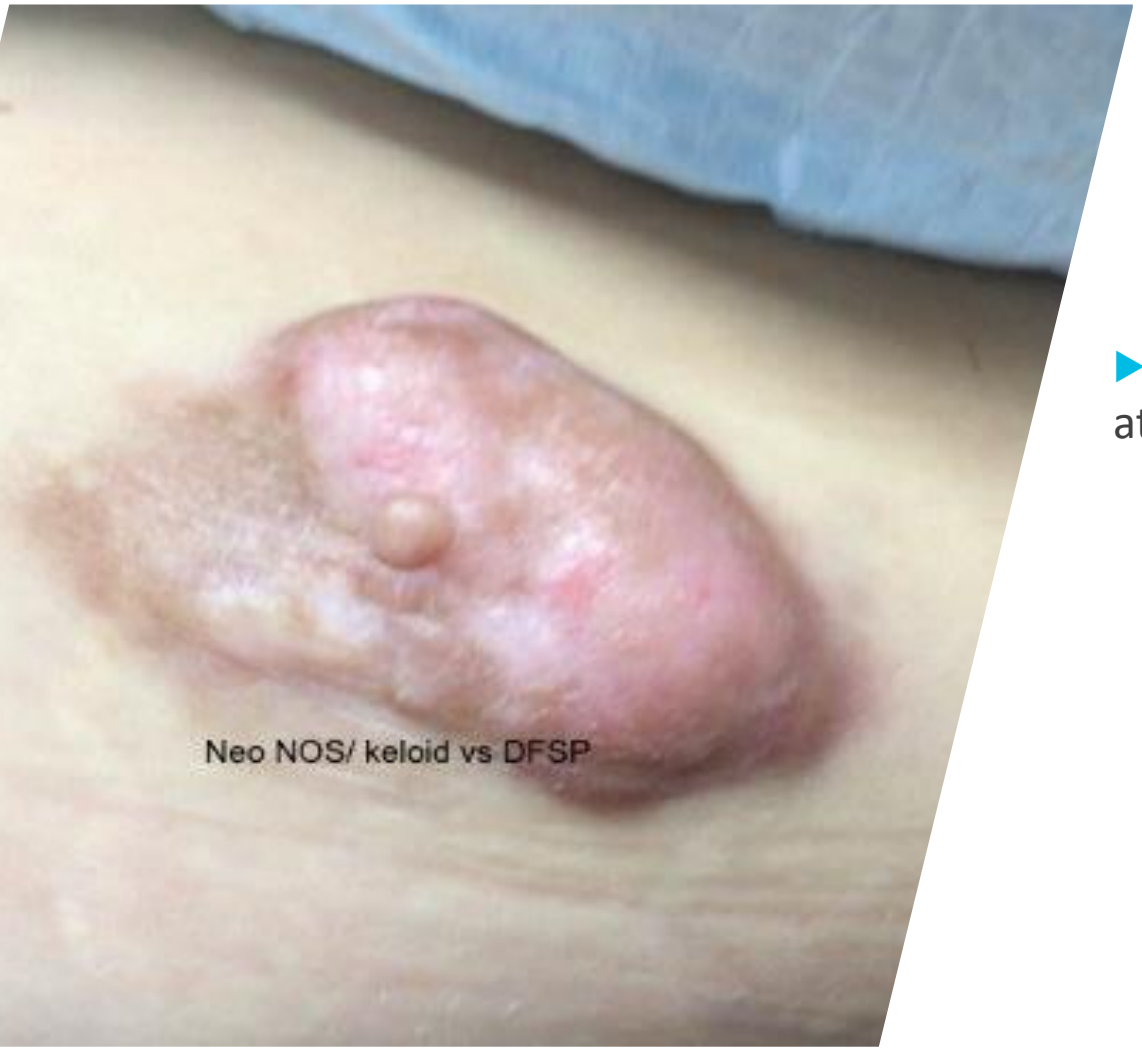
Neoadjuvant imatinib in DFSP

May be used in large DFSP or tumors in functionally or cosmetically crucial areas
Average tumor shrinkage 36-40%

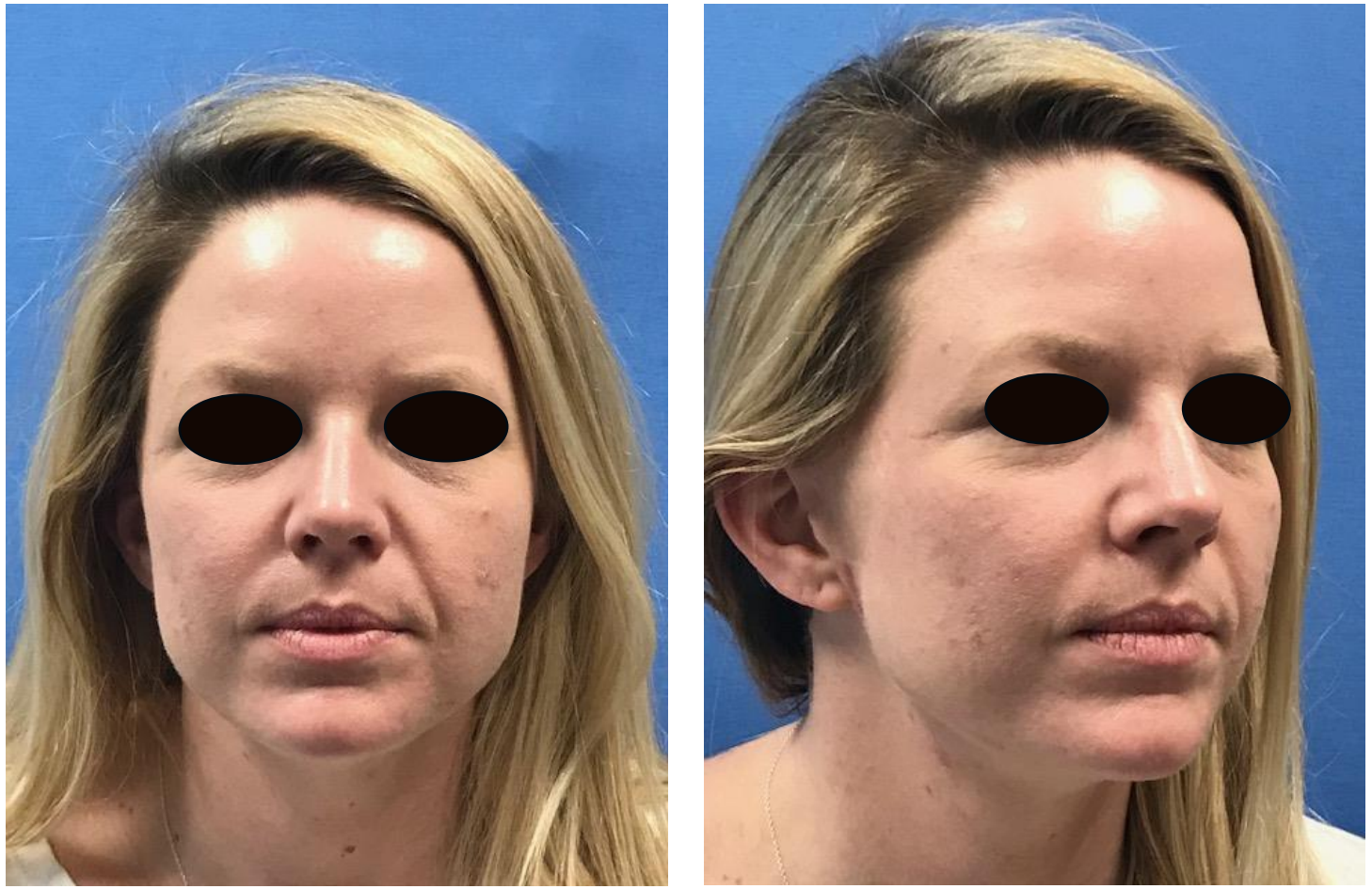
Table 1 Case reports of neoadjuvant imatinib in the treatment of primary dermatofibrosarcoma protuberans

Study	Disease site	Response	Outcome reported
Fontecilla *et al.*, 2017 [24]	Scalp with extension to periosteum	Partial response	Tumor completely resected
Bekerman *et al.*, 2013 [25]	Scapula	Not reported	Patient developed side effects of hypoxemia and shock requiring intubation. Tumor was resected with positive margins.
Lemm *et al.*, 2008 [26]	Scalp	Partial response	No evidence of recurrent disease after surgical resection
Wright and Petersen, 2007 [27]	Scalp	Partial response	No evidence of disease 16 months following resection
Savoia *et al.*, 2006 [28]	Anterior chest wall	Partial response	8 months of administration with continued reduction in tumor size
Mehrany *et al.*, 2006 [29]	Left cheek	Partial response	18 months following resection patient was disease-free

Dermatofibrosarcoma protuberans – the use of neoadjuvant imatinib for treatment of an uncommon breast malignancy: a case report. J Med Case Rep 2019;13:374.



- 39 yowf with 3 yr hx enlarging nodule at site of burn scar age 13



2-1-21 14 months s/p Mohs

Box 2. Principles of Radiotherapy (RT) for Microcystic Adnexal Carcinoma

Overall Considerations

- Protracted fractionation is associated with improved cosmesis
- Relative contraindications to RT include prior RT of the field, genetic conditions that predispose patients to radiosensitivity (eg, ataxia telangiectasia mutans), active connective tissue disease, and age <60 y

RT Monotherapy

- RT monotherapy is not preferred as first-line treatment. Surgically ineligible patients may be considered for RT alone. Doses of >64 Gy in 2-Gy fractions, or equivalent, should be considered (GRADE C)
- Because regional metastasis is rare, elective RT of the nodal basin is not recommended (GRADE B)

Postoperative Adjuvant Therapy

- Adjuvant RT (60 Gy in 2-Gy fractions over 4-6 wk) can be considered for high-risk or recurrent microcystic adnexal carcinoma when margins cannot be cleared surgically or there is persistence of occult tumor at the margins (GRADE B)

Squamoid Eccrine Ductal Carcinoma

- Exceedingly rare, first 3 cases reported in 1997
  - Wong et al Histopathology 1997; 30: 288–293
- Lim MM, Macdonald JA. Am J Dermatopathol 2022;44:249–253

Literature review of 50 cases

Avg age at presentation 75.7 years

Male:female 1.6:1.0

68% on head and neck, 22% extremities, 10% trunk

Local recurrence after WLE 25%, 0 % for 6 cases treated with MMS

Lymph node mets 14%, distant mets 5%

No defined margins for excision, imaging workup or XRT recommendations (2 cases received adjunct XRT for pos margins and LVSI)

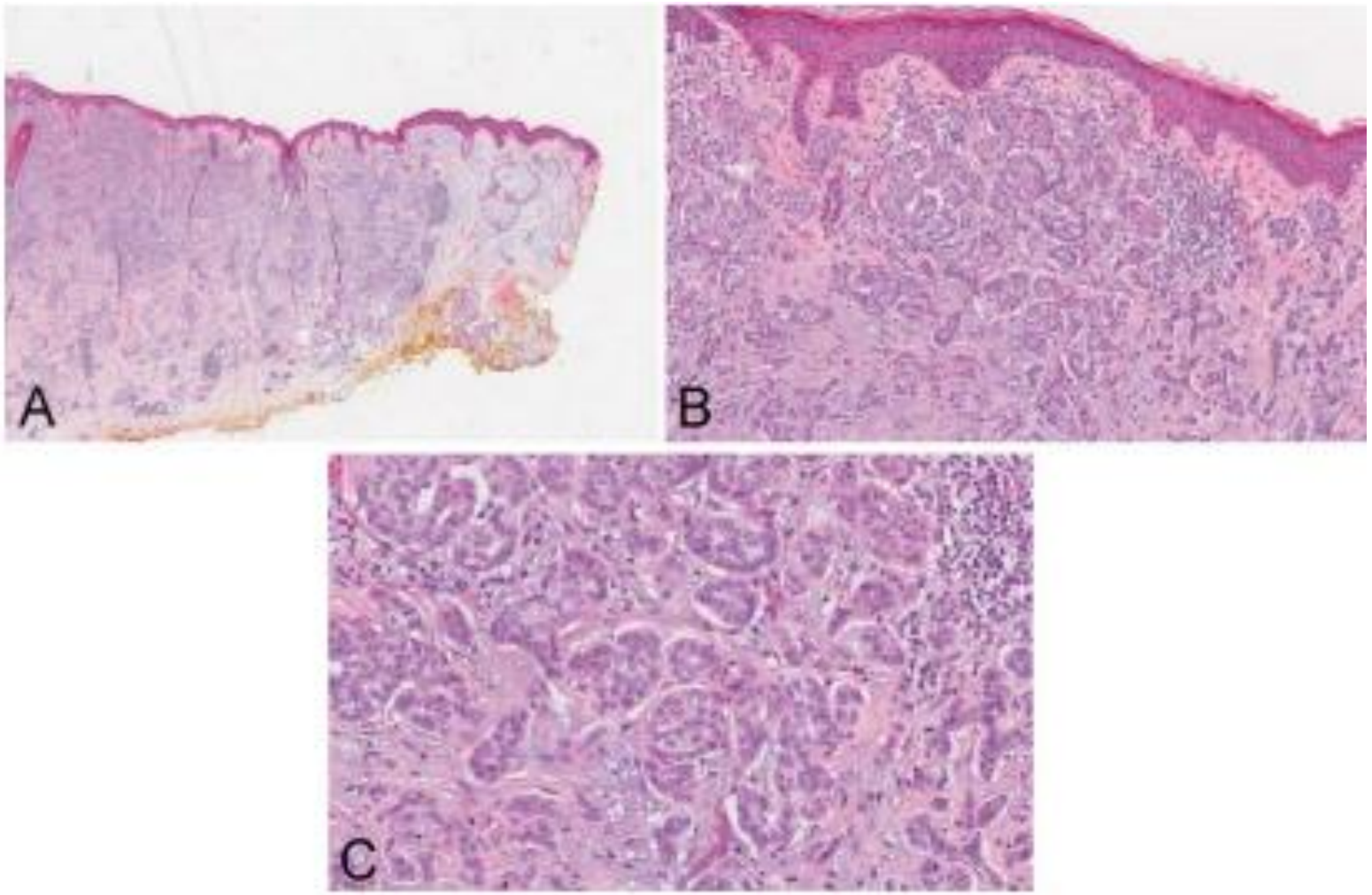
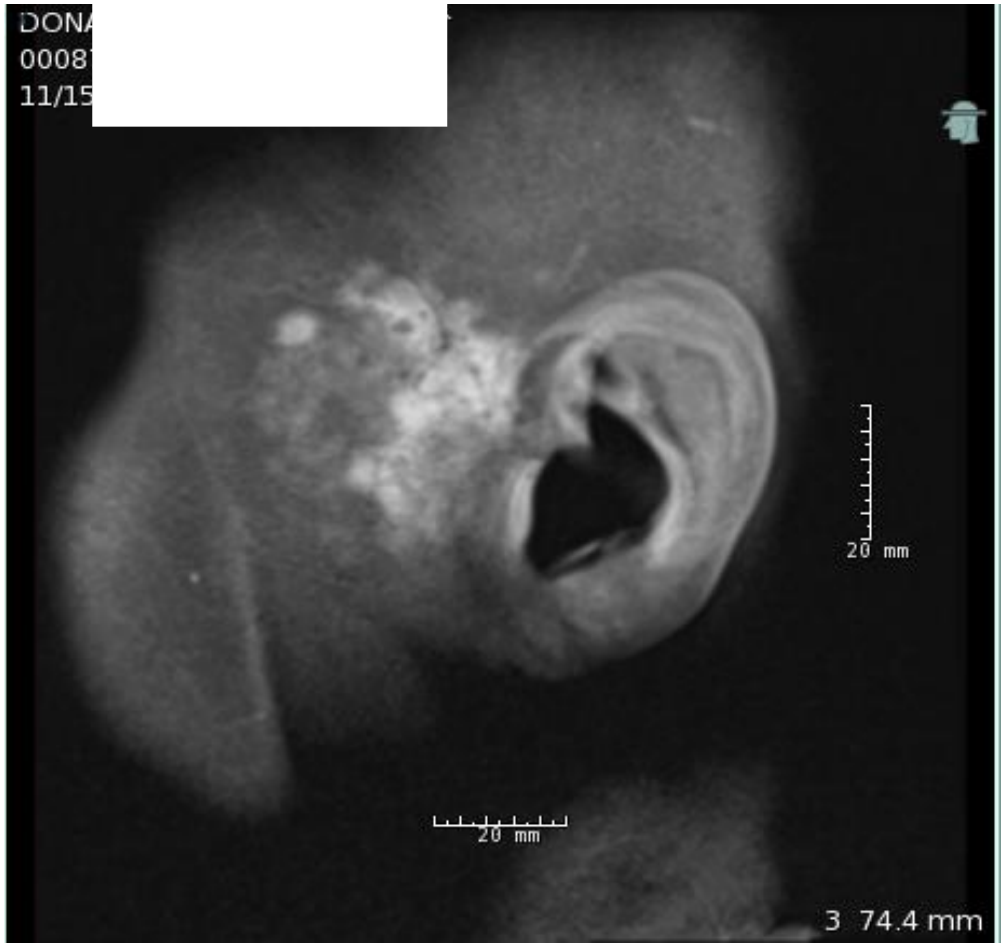
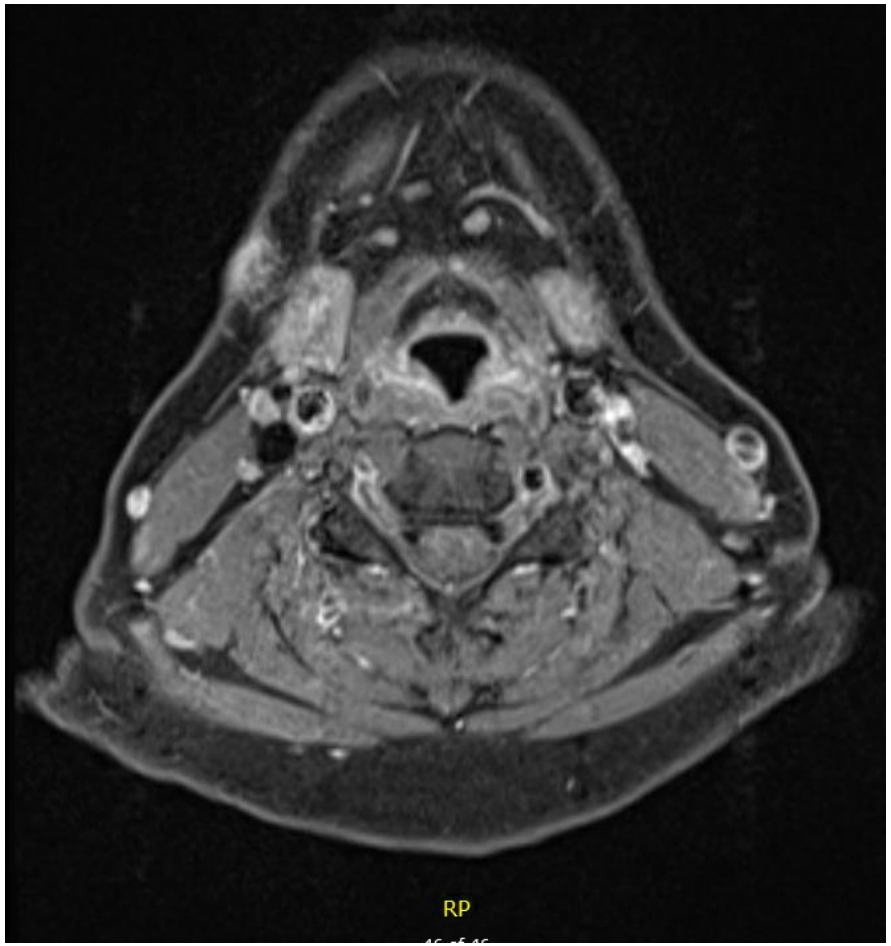


FIGURE 1. SEDC. A, A low-power view showing a deeply infiltrating tumor with squamoid and ductal differentiation in (B, C).

Lim et al.





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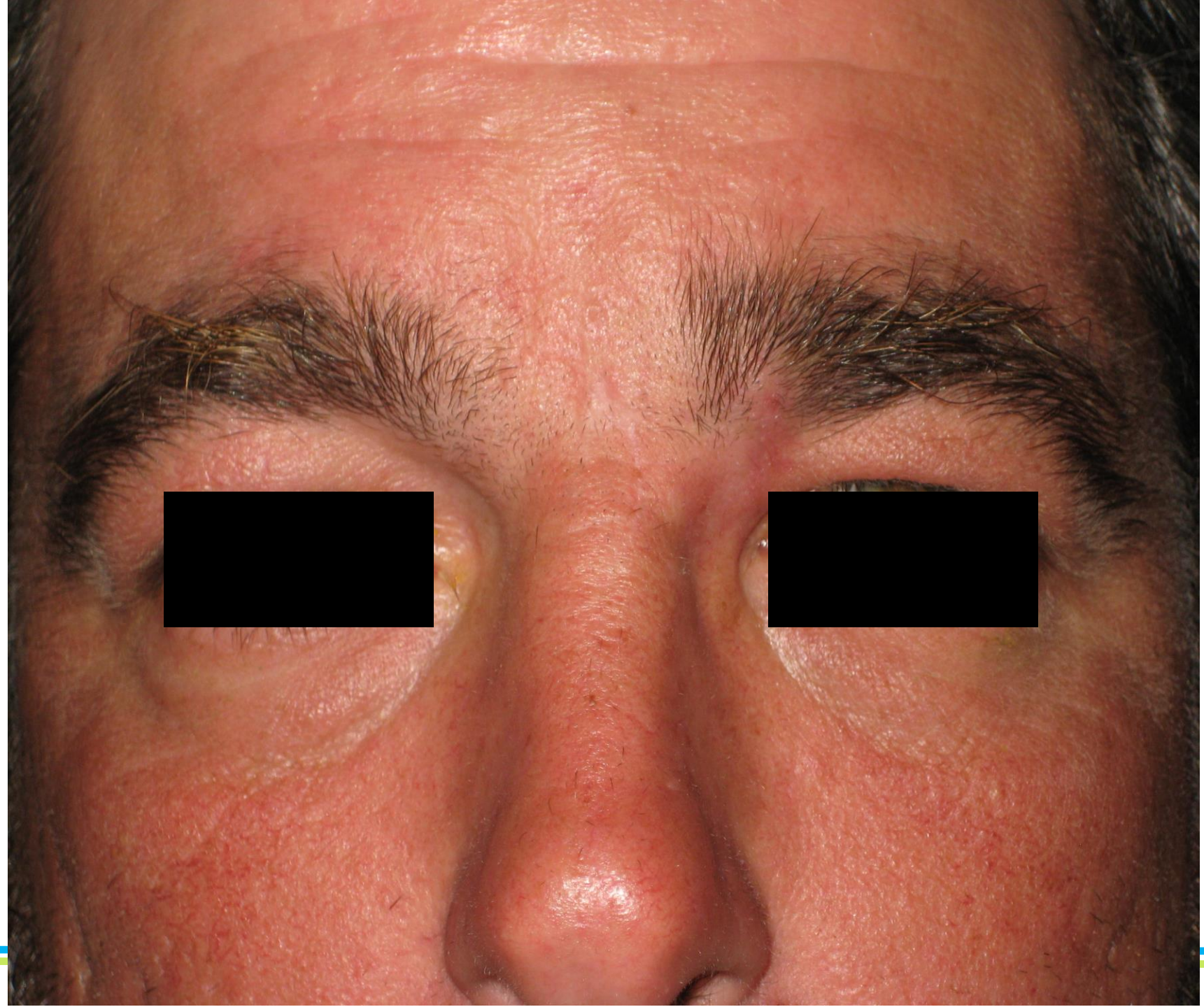
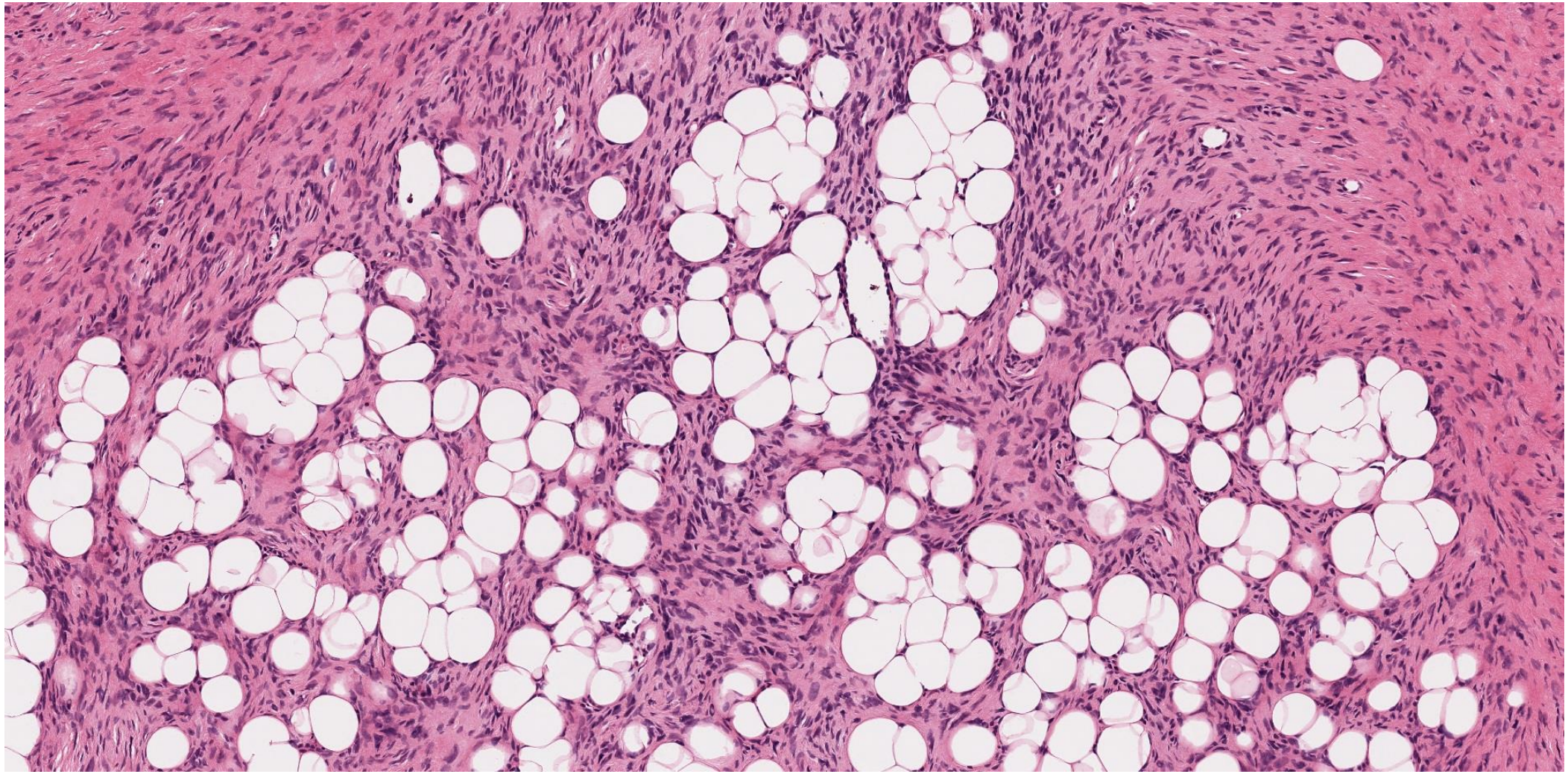
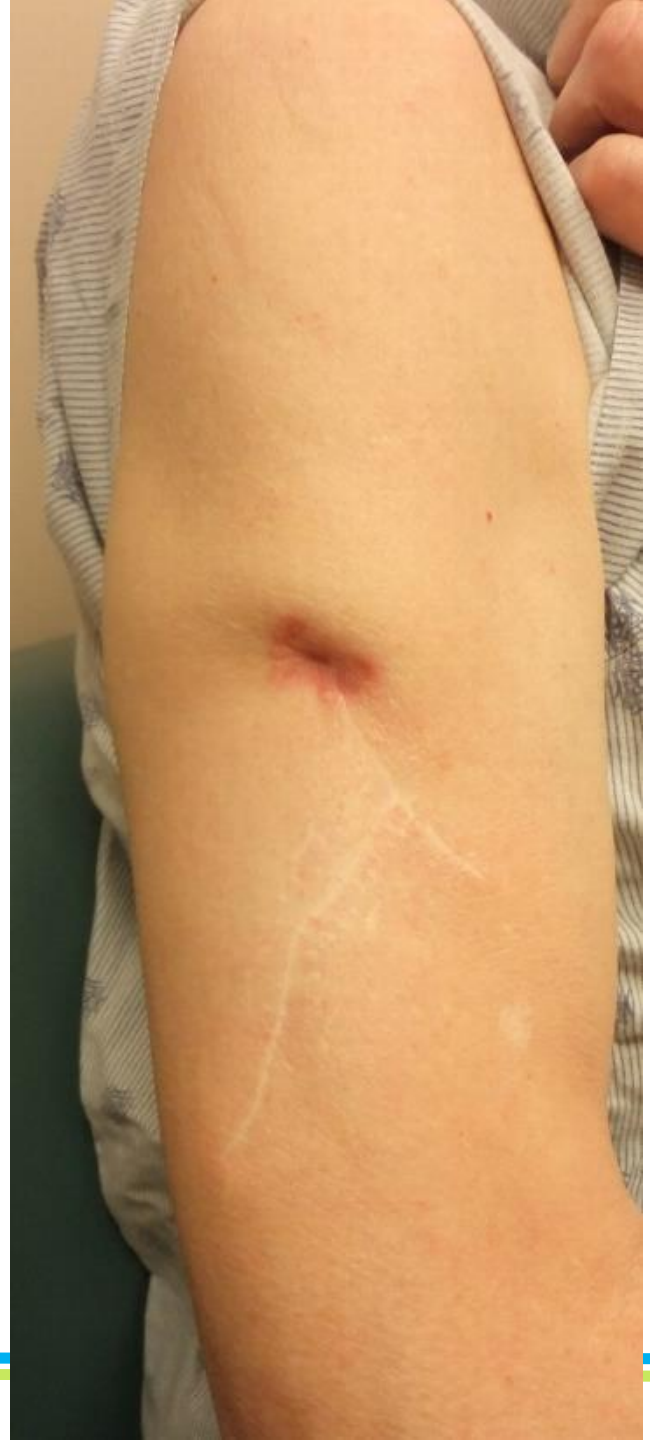


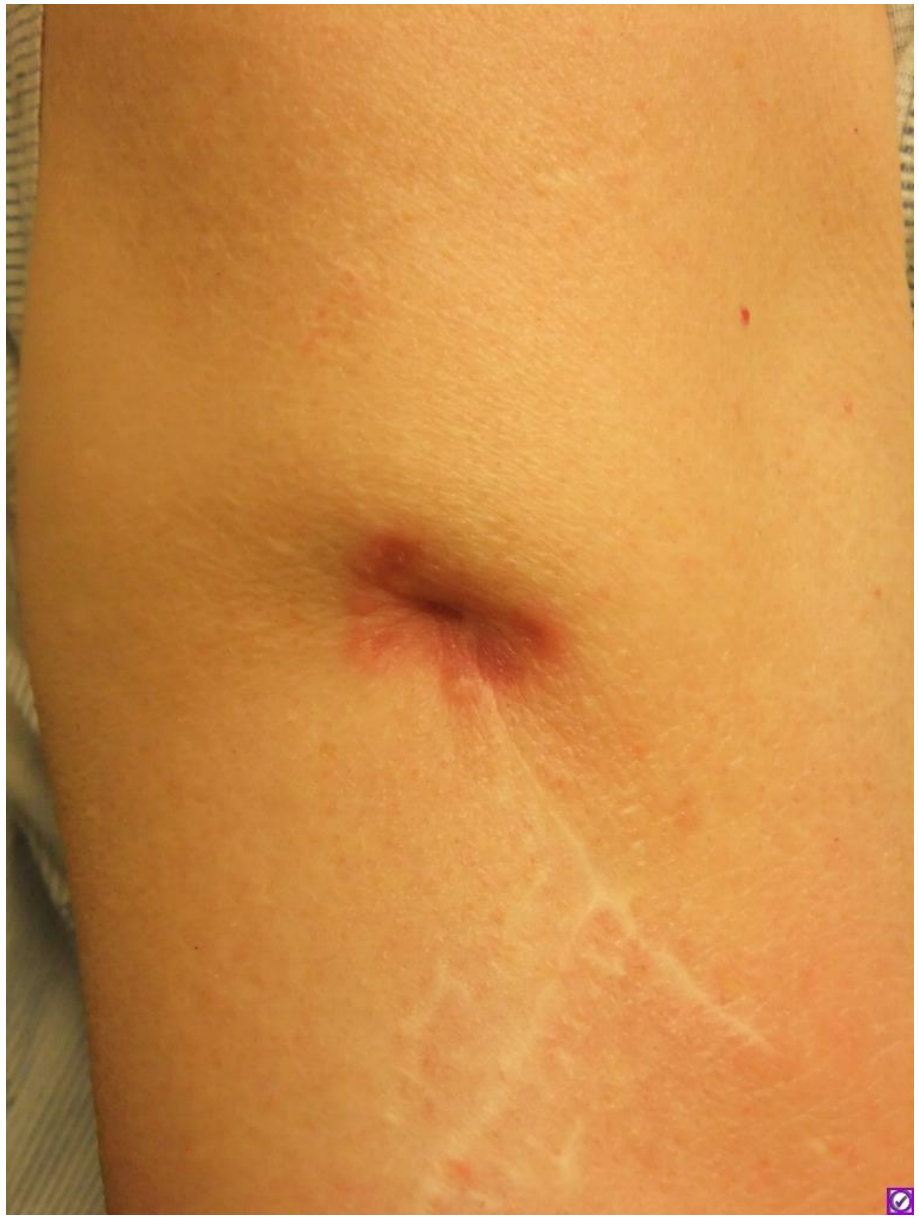


CD 34+, S100-

History

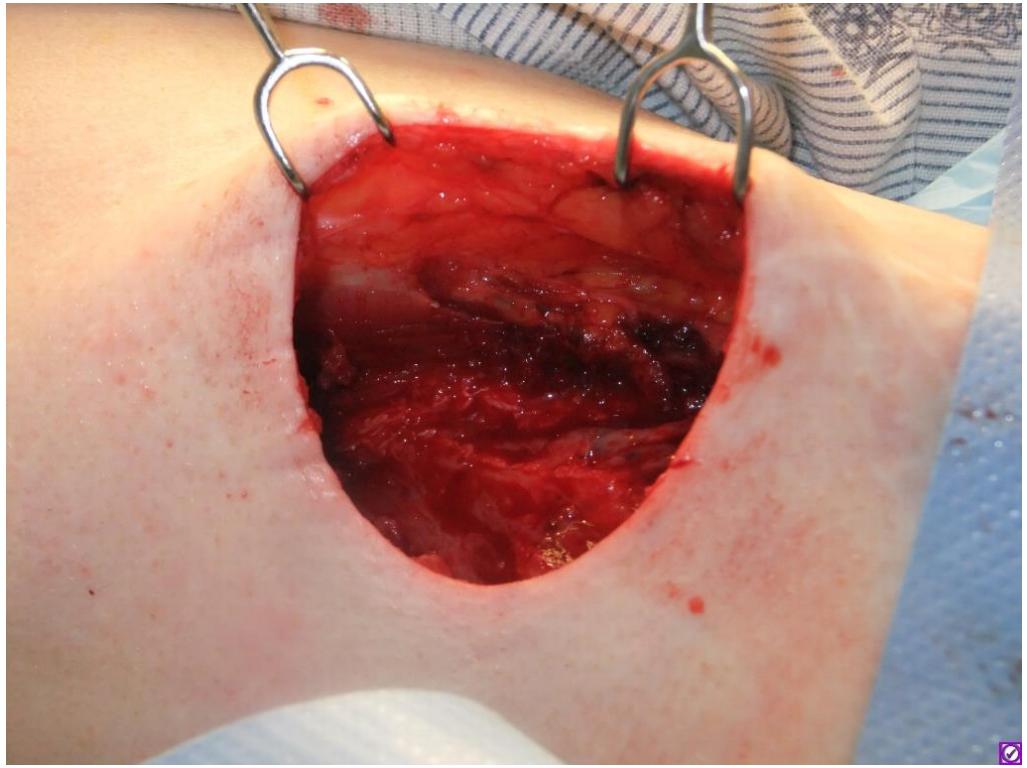
- 63 yowm with multiply recurrent BCC right upper lateral arm, s/p EDC, excision, MMS 2001 and 2006
- Punch biopsy 12/2012 = infiltrative BCC

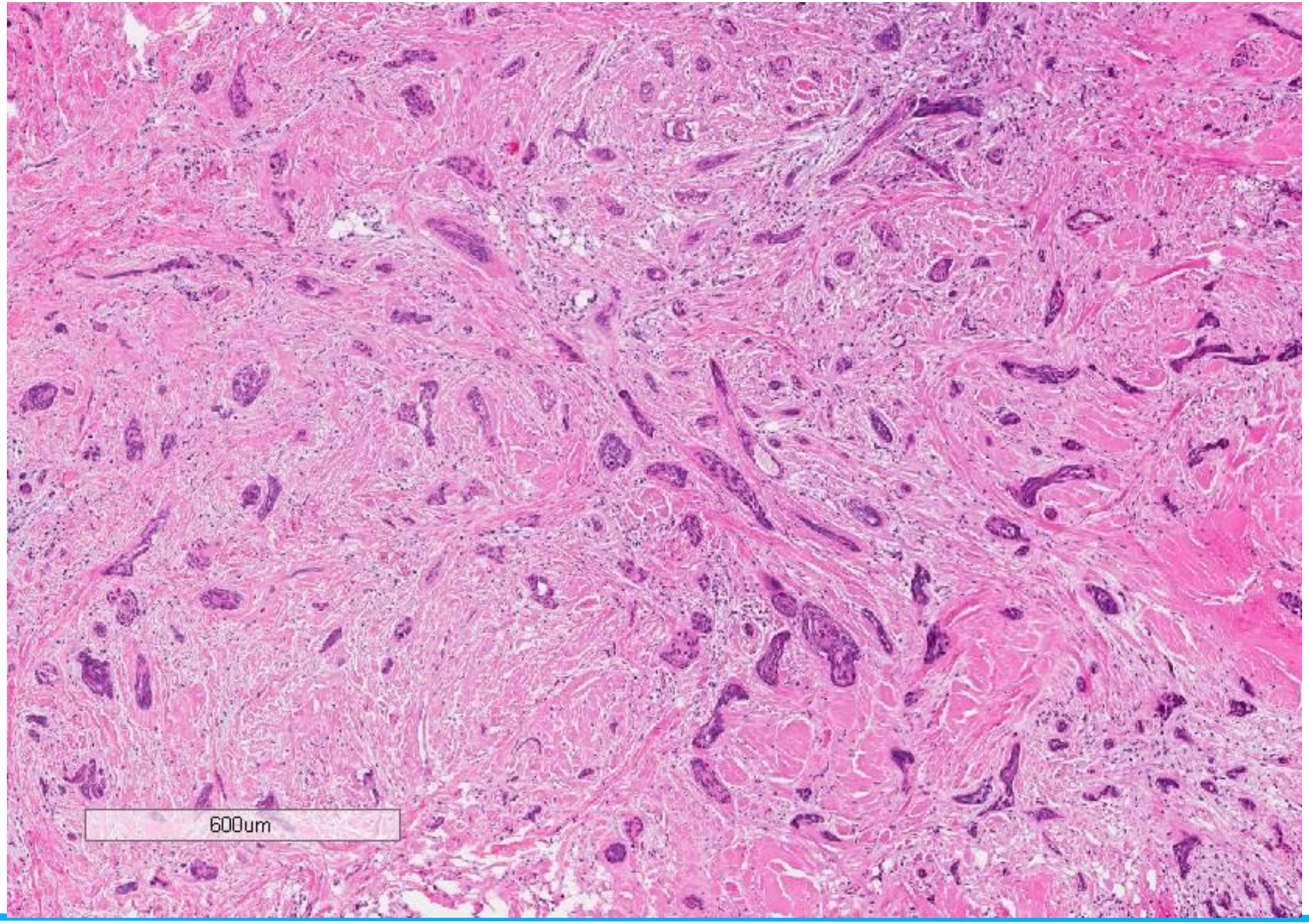


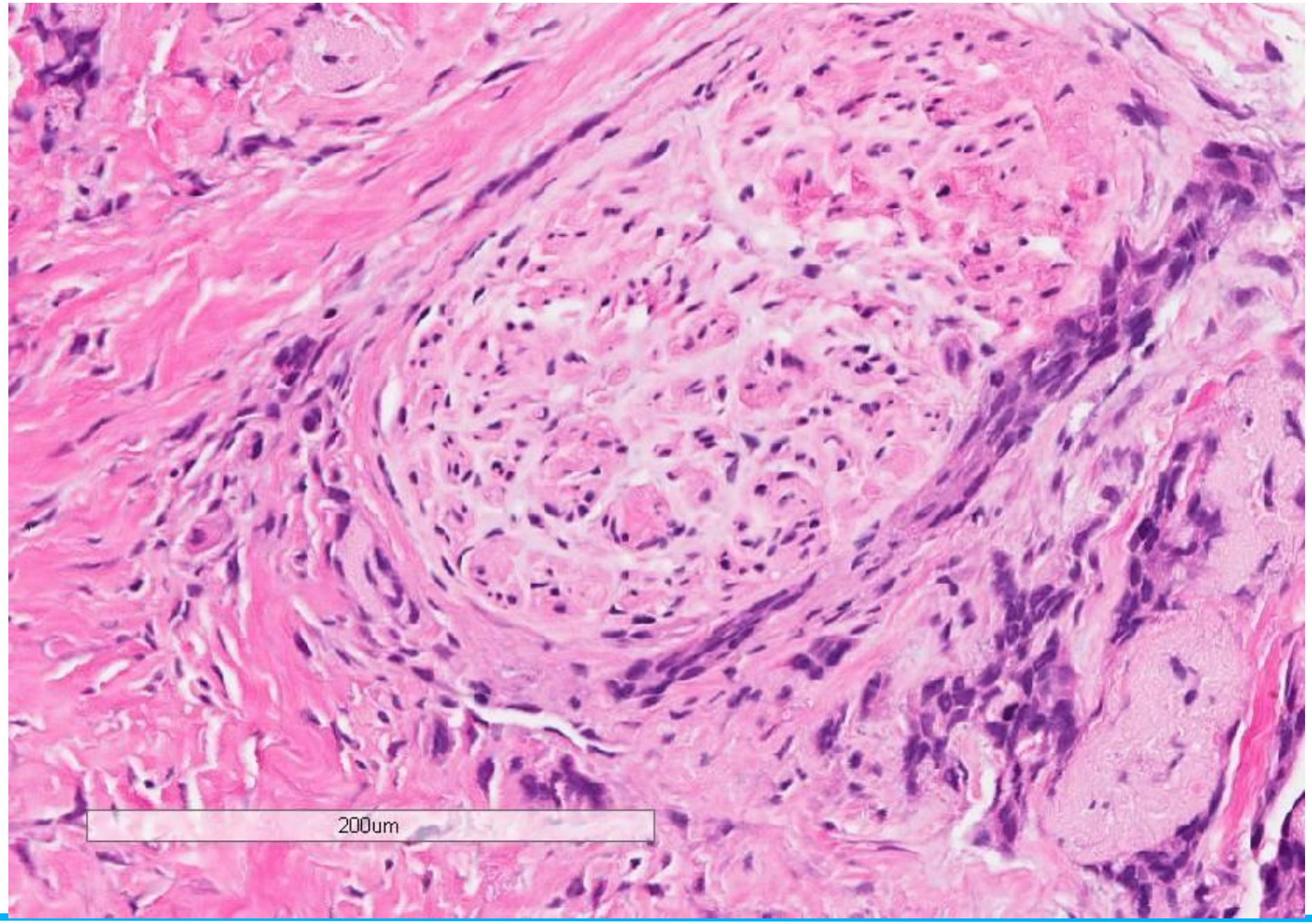


History

- Mohs surgery – infiltrative tumor involved deep subcutaneous tissue, muscle and periosteum of humerus, extensive perineural tumor

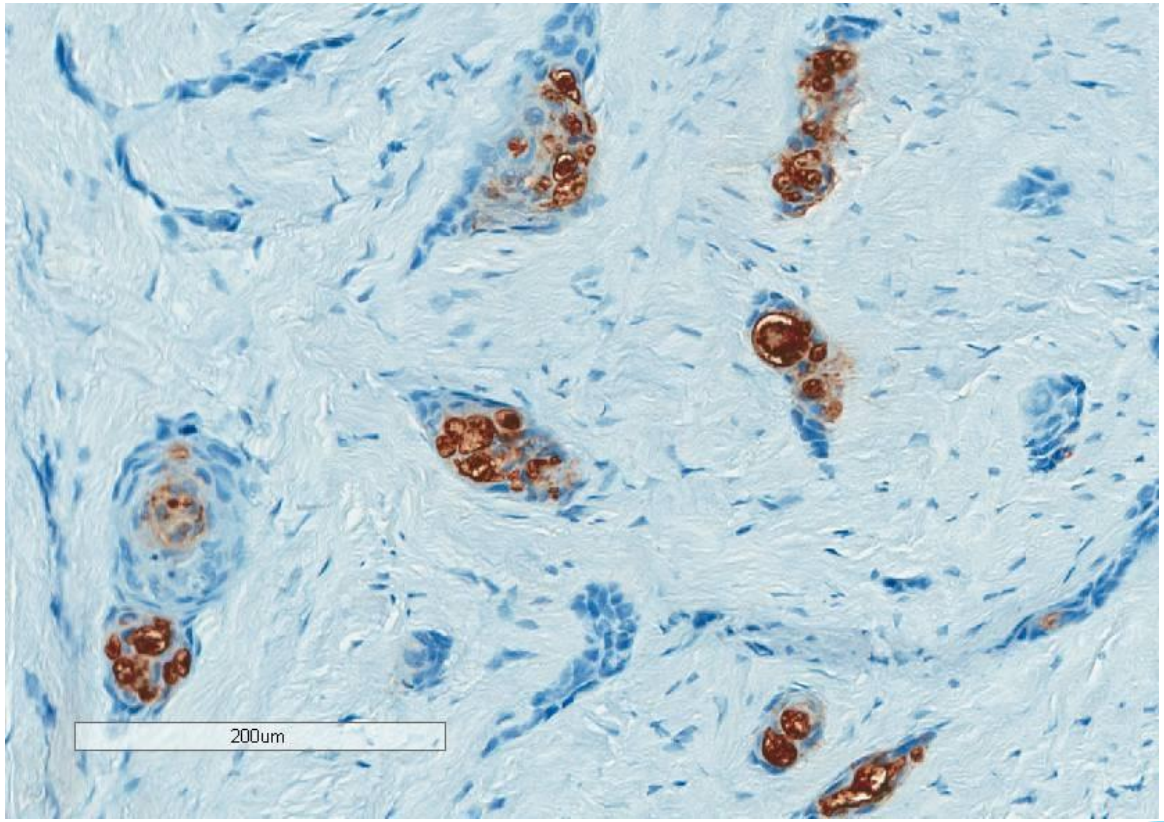



600um


200um

History

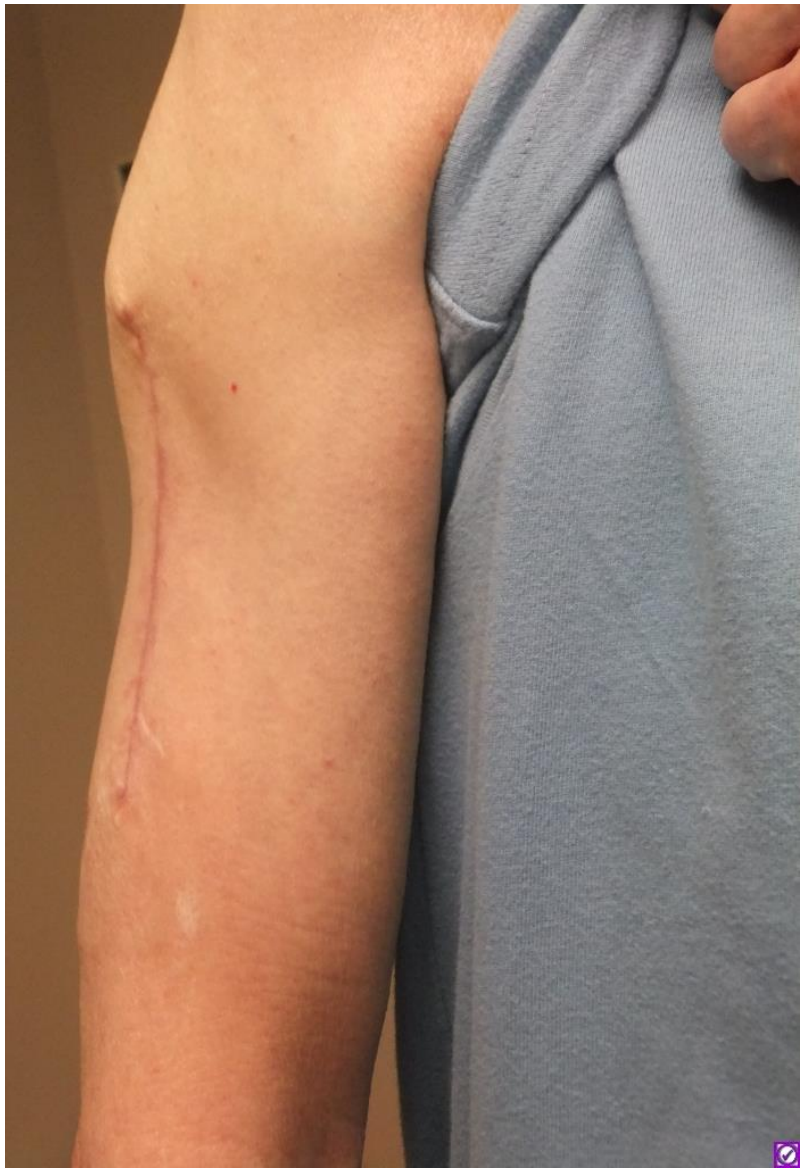
- Nonmarginal tissue sent for permanent sections CEA+, BerEP4- c/w microcystic adnexal carcinoma (MAC)



CEA

History

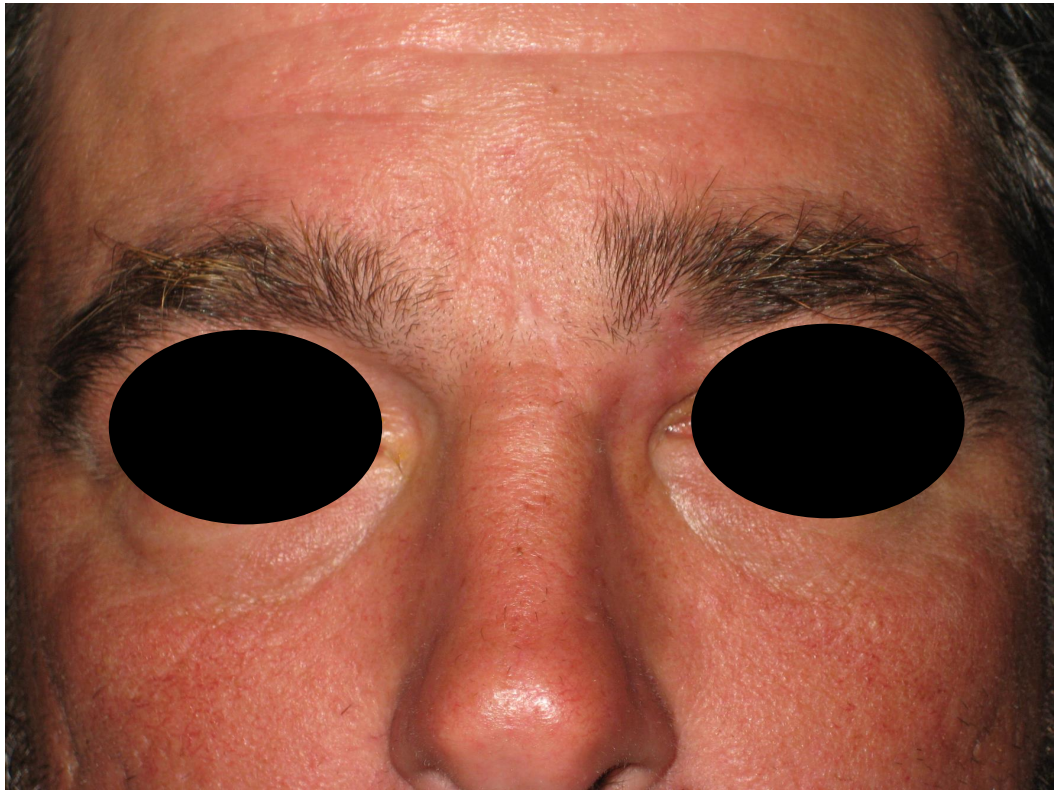
- Plastic surgeon excised adherent soft tissue and outer table of humerus, primary closure
- MAC involved periosteum, outer table clear



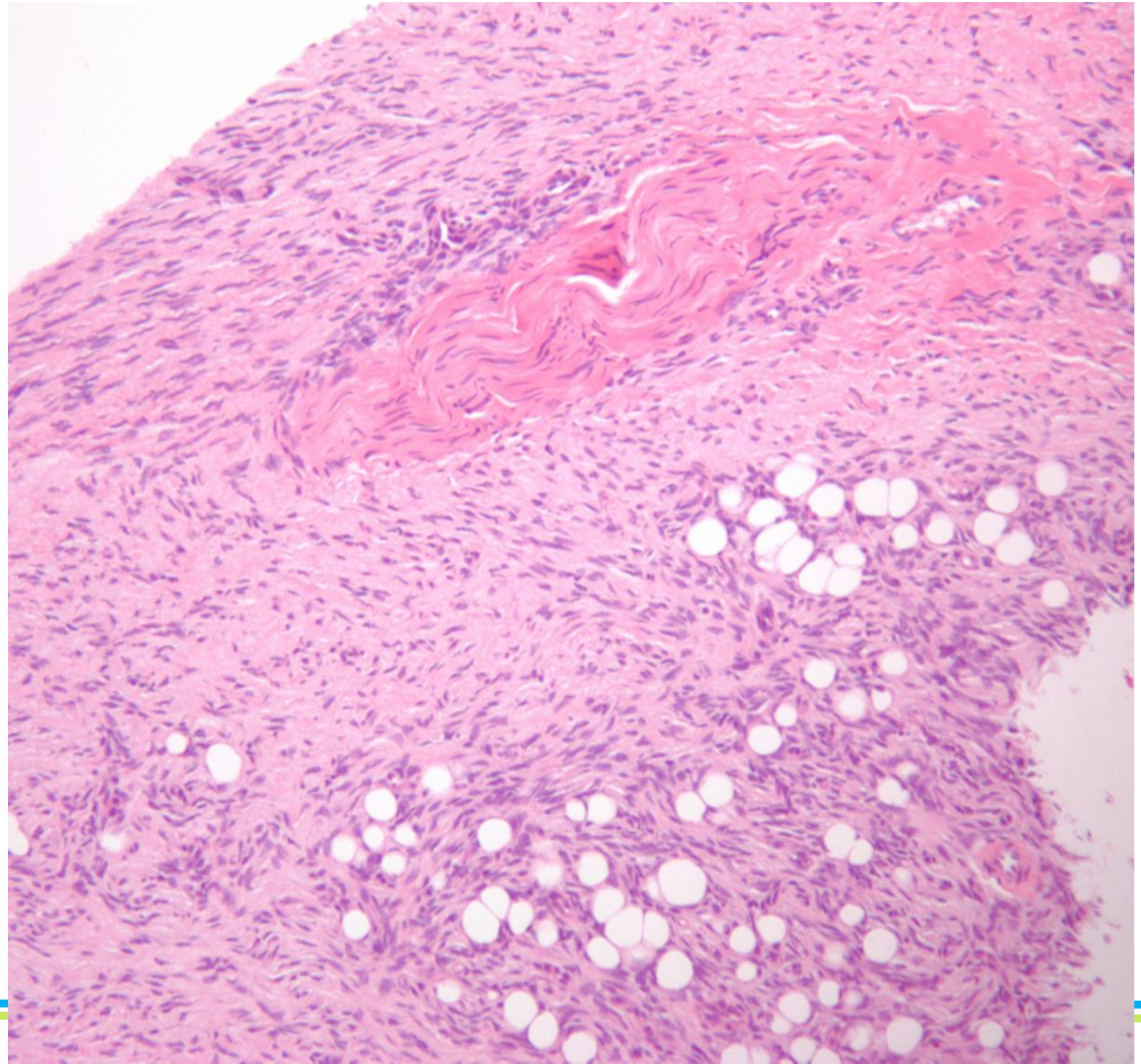
18 months NED

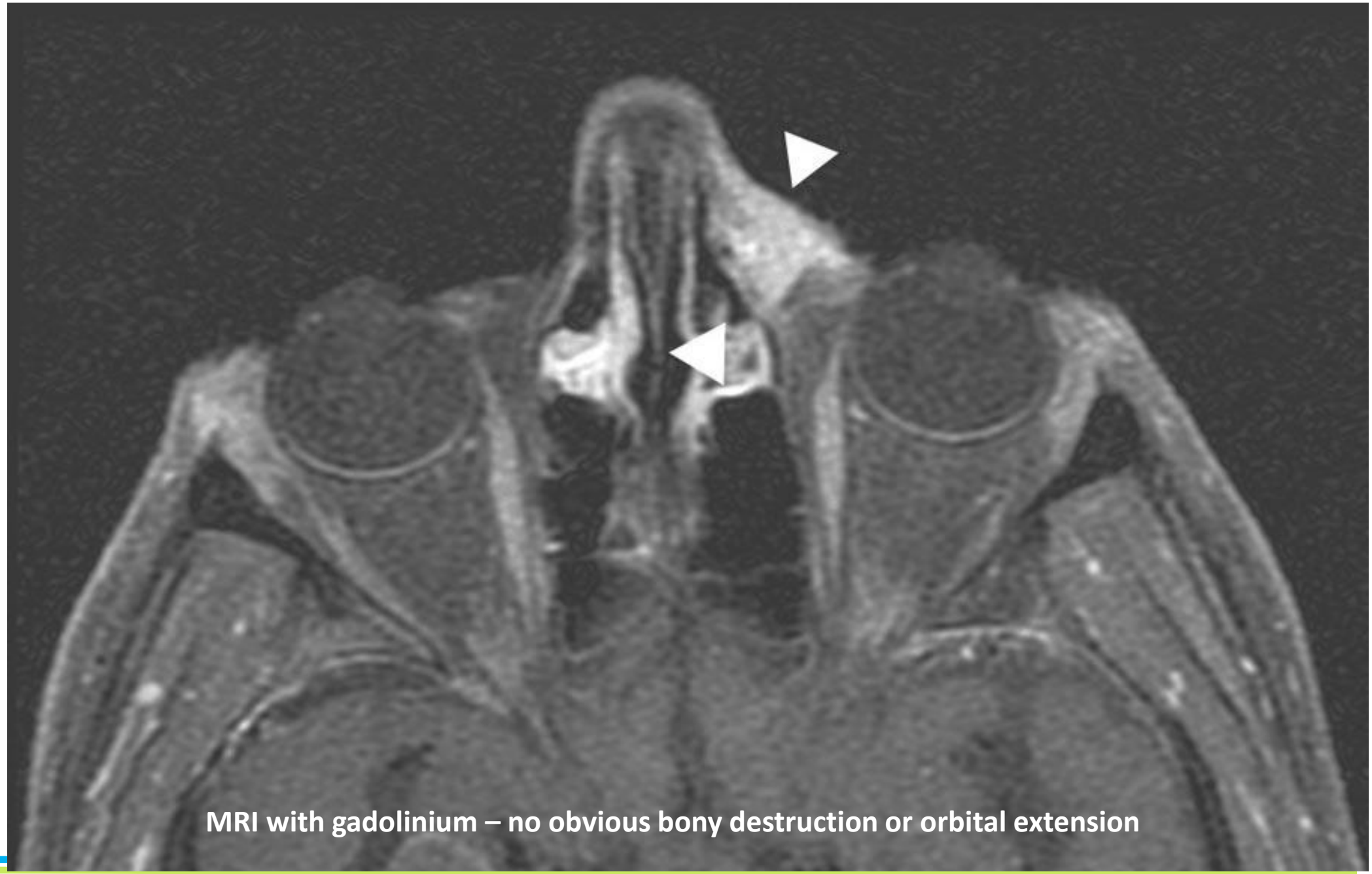
HISTORY

- 38 yowm slow growing firm mass below left eyebrow
- Prior history of blunt trauma to this site 2 years prior



Goshe JM et al. Ophthal Plast Reconstr Surg 2012; 28: e65-7.





MRI with gadolinium – no obvious bony destruction or orbital extension

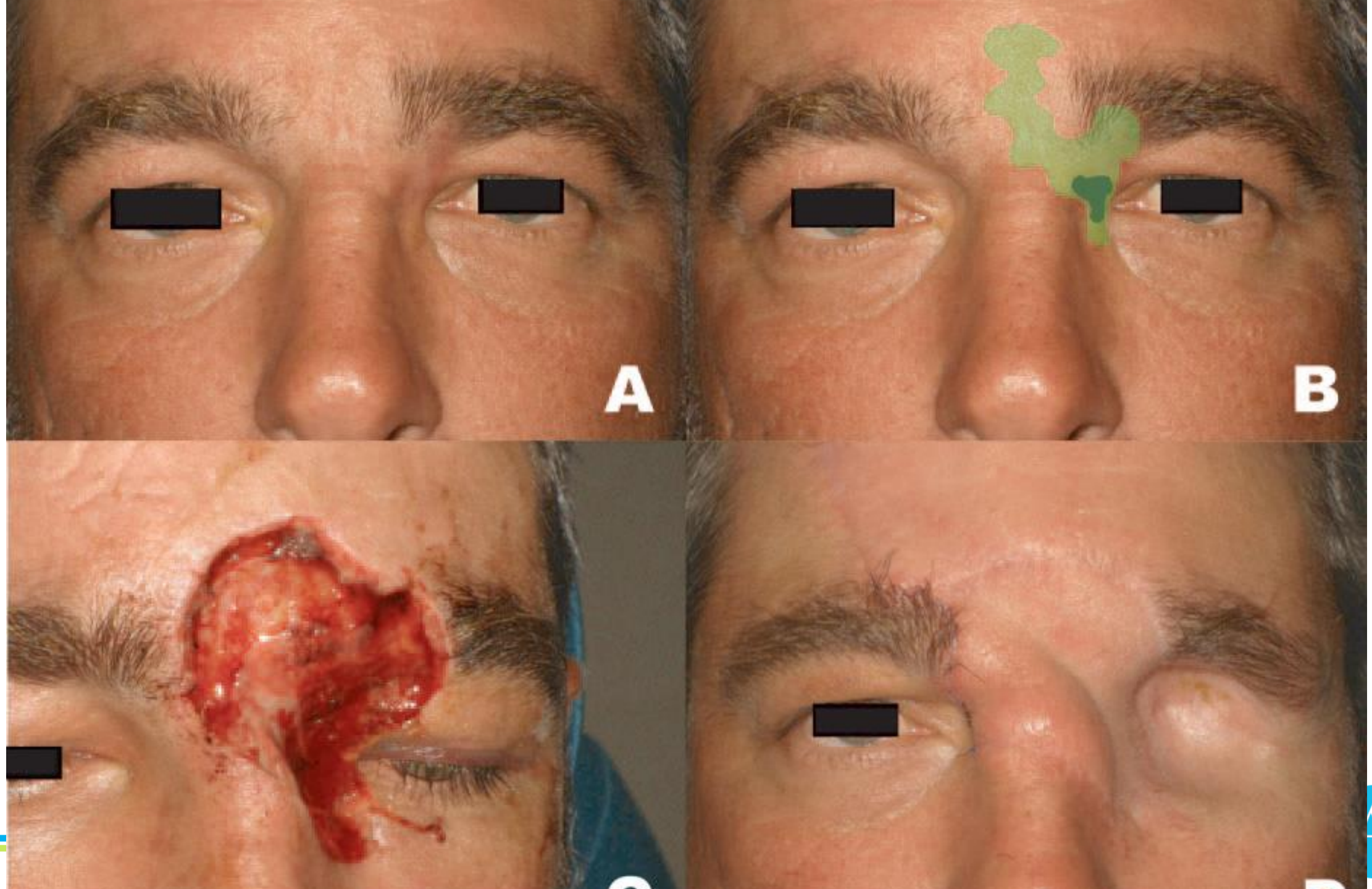
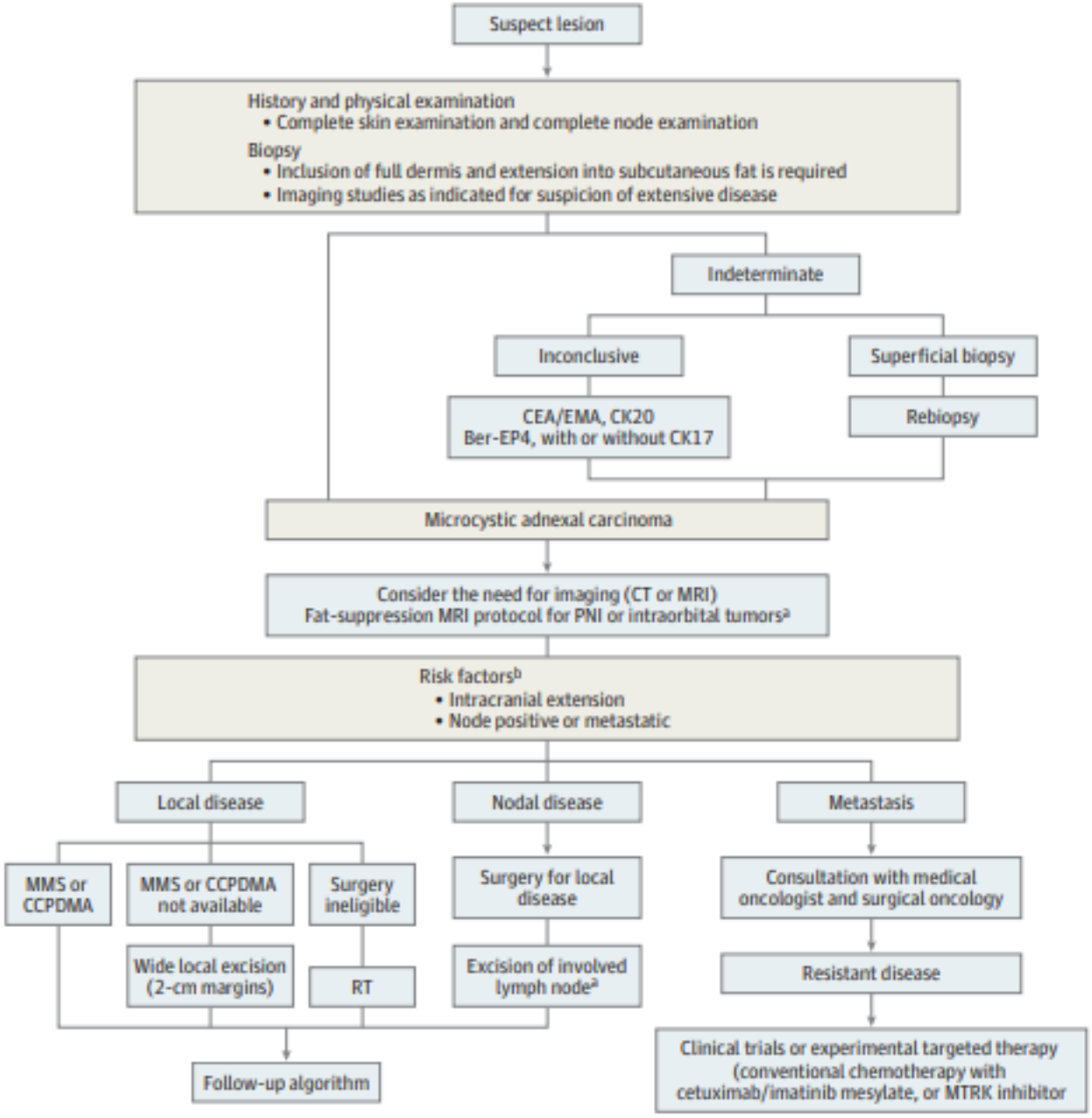

A
B

Figure 2. Clinical Management and Initial Treatment Algorithm for Microcystic Adnexal Carcinoma



CCPDMA indicates complete circumferential peripheral and deep margin assessment; CEA, carcinoembryonic antigen; CT, computed tomography; EMA, epithelial membrane antigen; MMS, Mohs micrographic surgery; MRI, magnetic resonance imaging; MTRK, multitargeted tyrosine receptor kinase; PNI, perineural invasion; RT, radiotherapy.

[a] There is no evidence to support completion neck dissection for a positive lymph node at presentation. Both nodal and metastatic disease should also receive surgery as per the local disease pathway.

[b] No factor linked to worse prognosis (more data required).

Worley B et al. Evidence-Based Clinical Practice Guidelines for Microcystic Adnexal Carcinoma. Informed by a Systematic Review. JAMA Dermatol 2019; 155: 1059-1068.

Imatinib
Side effects

- The most common adverse events are mucocutaneous (7%-88.9%)
- edema
- maculopapular eruption
- pruritus
- alopecia
- xeroderma
- lichenoid reactions
- pigmentary disorders of skin
- Nail and mucosal hyperpigmentation
- psoriasiform reactions; pityriasis rosealike eruption; acute generalized exanthematous pustulosis; Stevens-Johnson syndrome/toxic epidermal necrolysis; neutrophilic dermatosis; and photosensitivity, among others
- fever
- muscle cramps
- abdominal pain
- diarrhea
- nausea and vomiting
- fatigue
- headache
- musculoskeletal pain,
- anemia , neutropenia, thrombocytopenia
- hyperglycemia
- electrolyte disturbance
- liver enzyme elevation

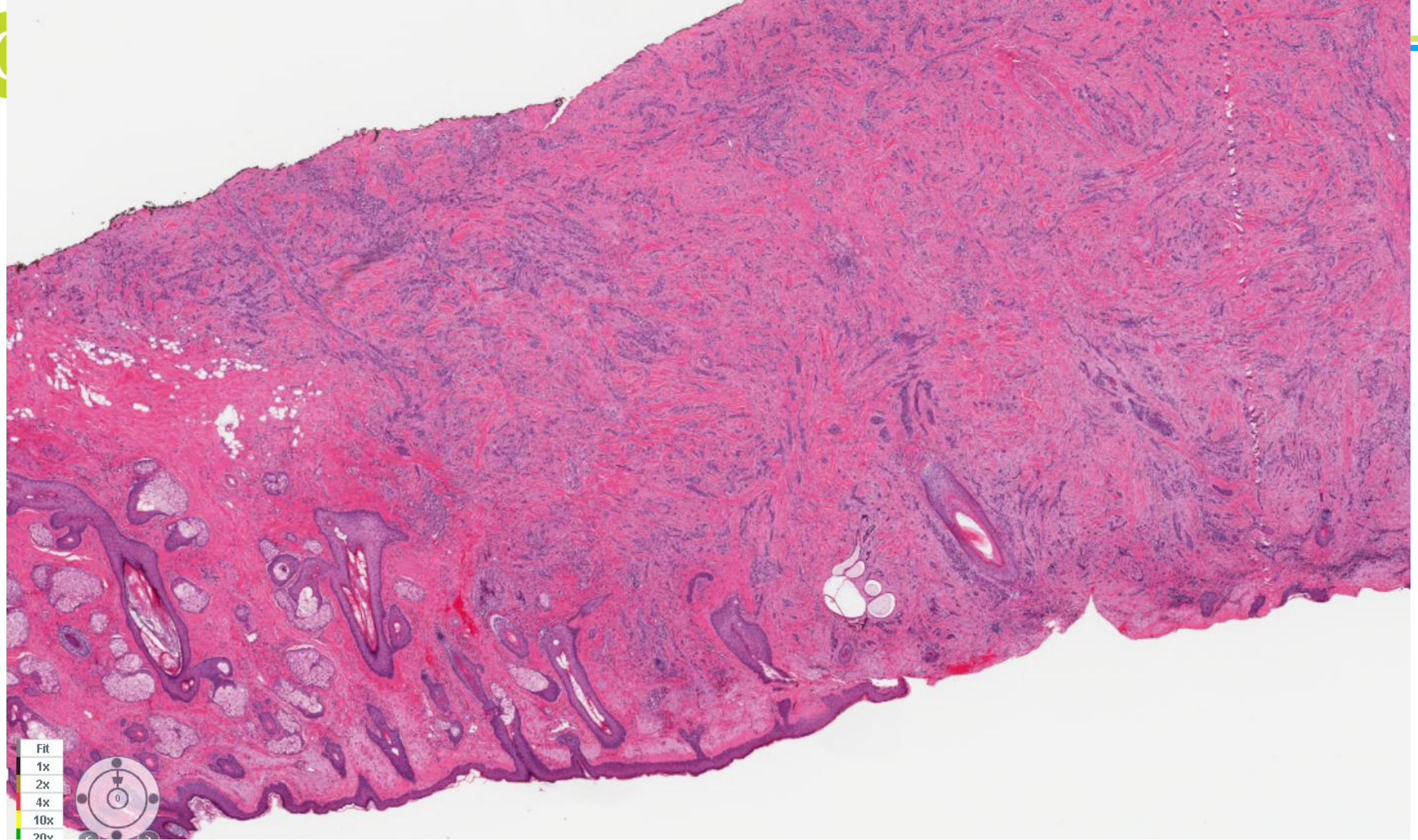

Fit
1x
2x
4x
10x
20x

TABLE 4. Key Distinctive Histologic Features of SEDC and Its Mimickers

	SEDC	Eccrine Syringoid Carcinoma	Microcystic Adnexal Carcinoma
Squamous pearls	+	−	+
Squamous eddies	+	−	−
Aggressive growth pattern	++	+	++
Tubular/ductal structures with atypical cells	+	++ (basaloid cells)	++ (squamoid > basaloid cells)
Syringoma-like ducts	−	+ (larger)	+ (smaller)
Sclerotic stroma	+	−	+
Mucin	−	+ (variable)	−
Perineural invasion	++	+	++

Lim, Megan M., and Jillian A. Macdonald. "Squamoid Eccrine Ductal Carcinoma: Treatment and Outcomes." The American Journal of Dermatopathology 44.4 (2022): 249-253.

Squamoid Eccrine Ductal Carcinoma

Histology

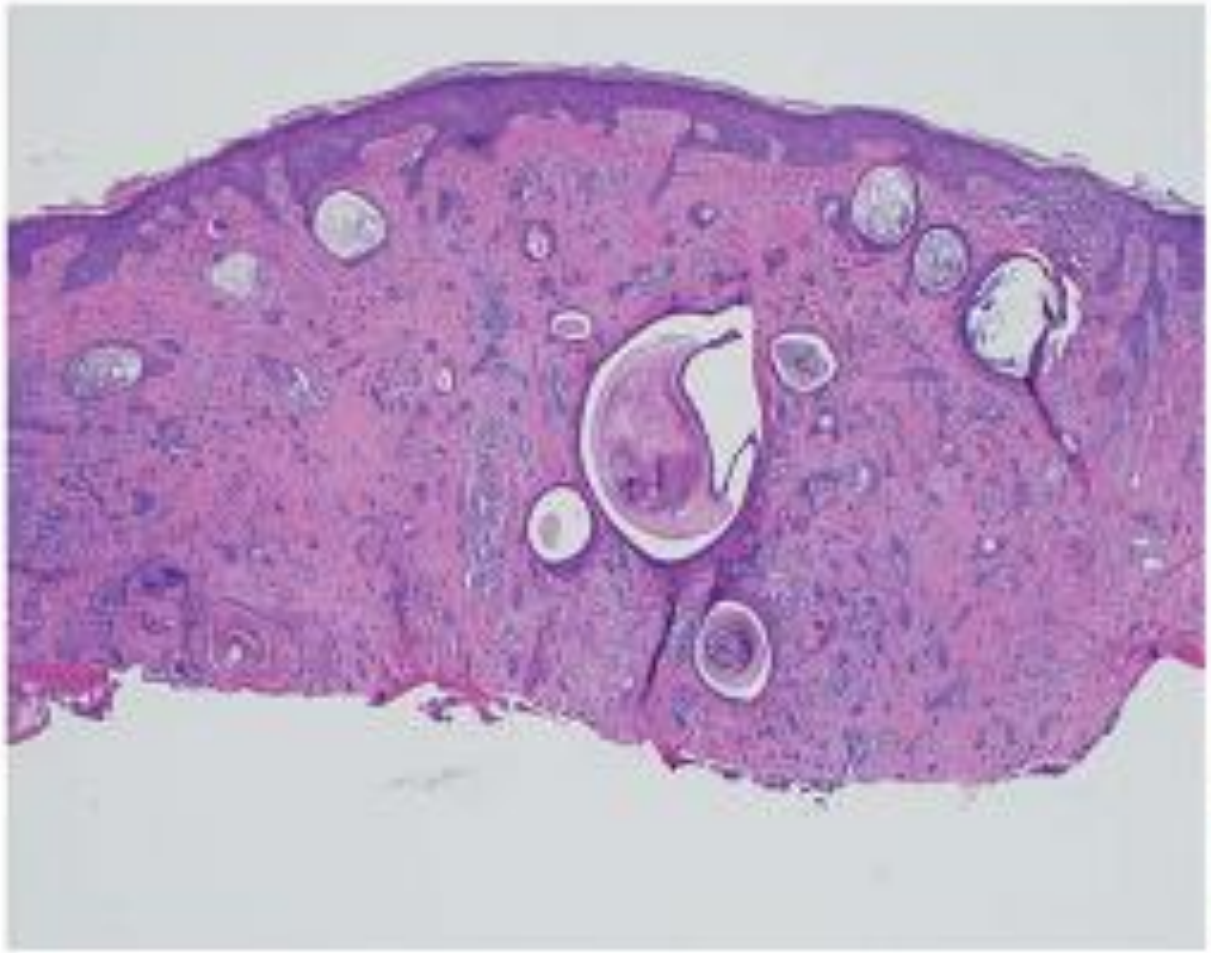
Characteristic biphasic appearance

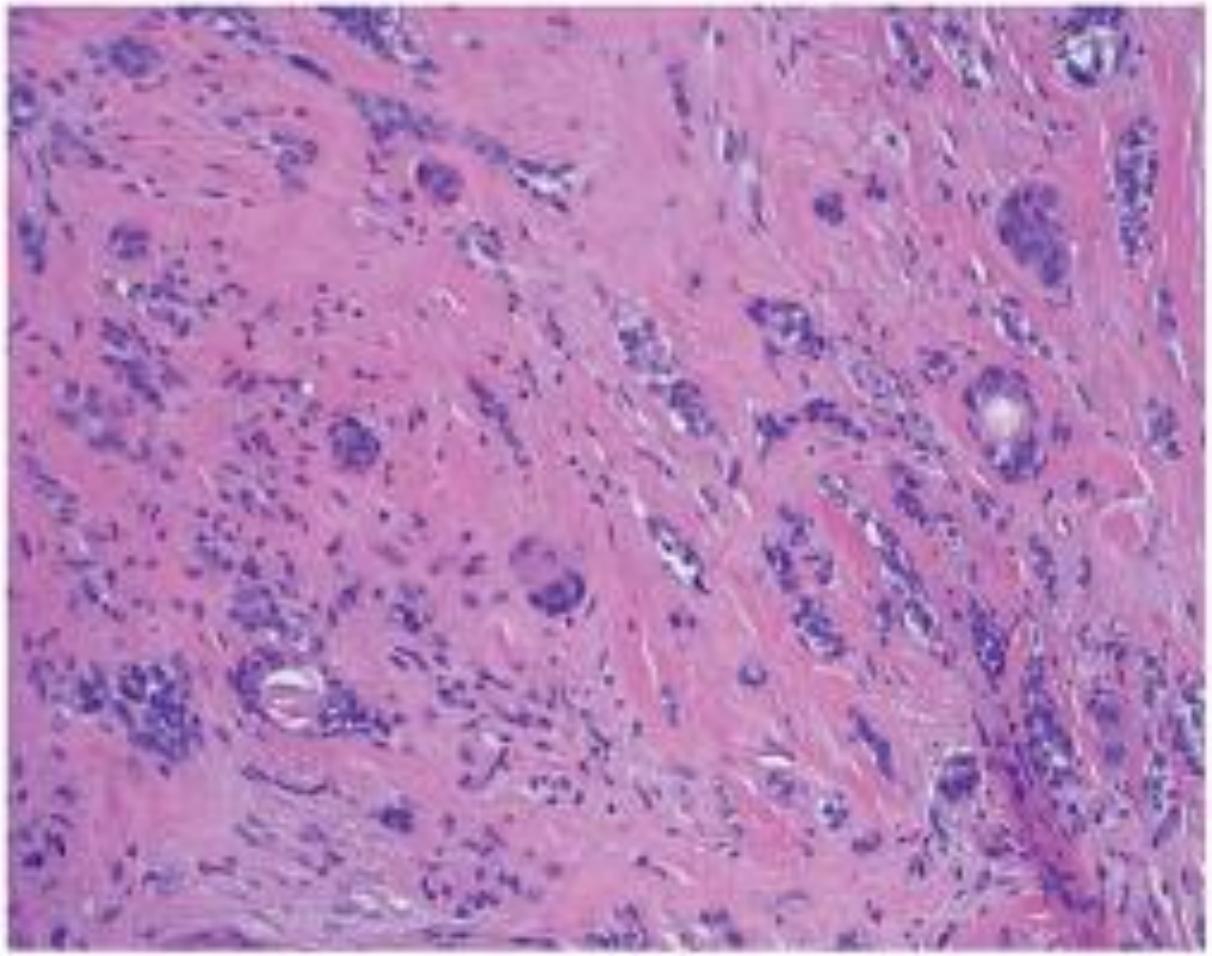
- Poorly circumscribed tumor with infiltrative growth pattern, deep extension into dermis and subcutaneous fat
- **Prominent squamous differentiation most apparent superficially** where neoplastic aggregates are larger and composed of epithelial cells with abundant amphophilic cytoplasm, may have epidermal connection and SCCIS and/or AK
- In central and **deep portions of tumor neoplastic aggregates are basaloid , angulated** and display **focal syringomatoid features with tubular structures** reminiscent of a benign syringoma in a desmoplastic OR myxoid stroma
- Cystic structures reminiscent of MAC have NOT been described in SEDC
- Ductal lumina with distinct eosinophilic cuticles are seen in many tumor aggregates
- Cellular pleomorphism, atypia and mitoses are present

Squamoid Eccrine Ductal Carcinoma

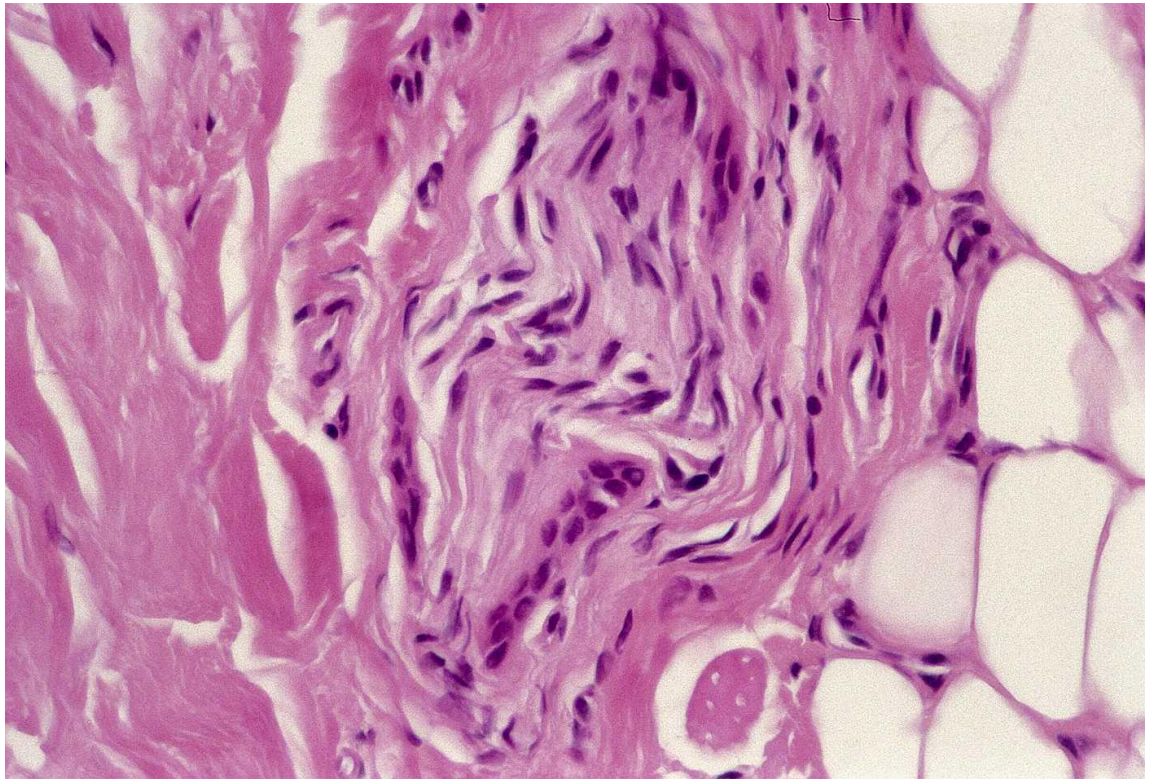
Histology

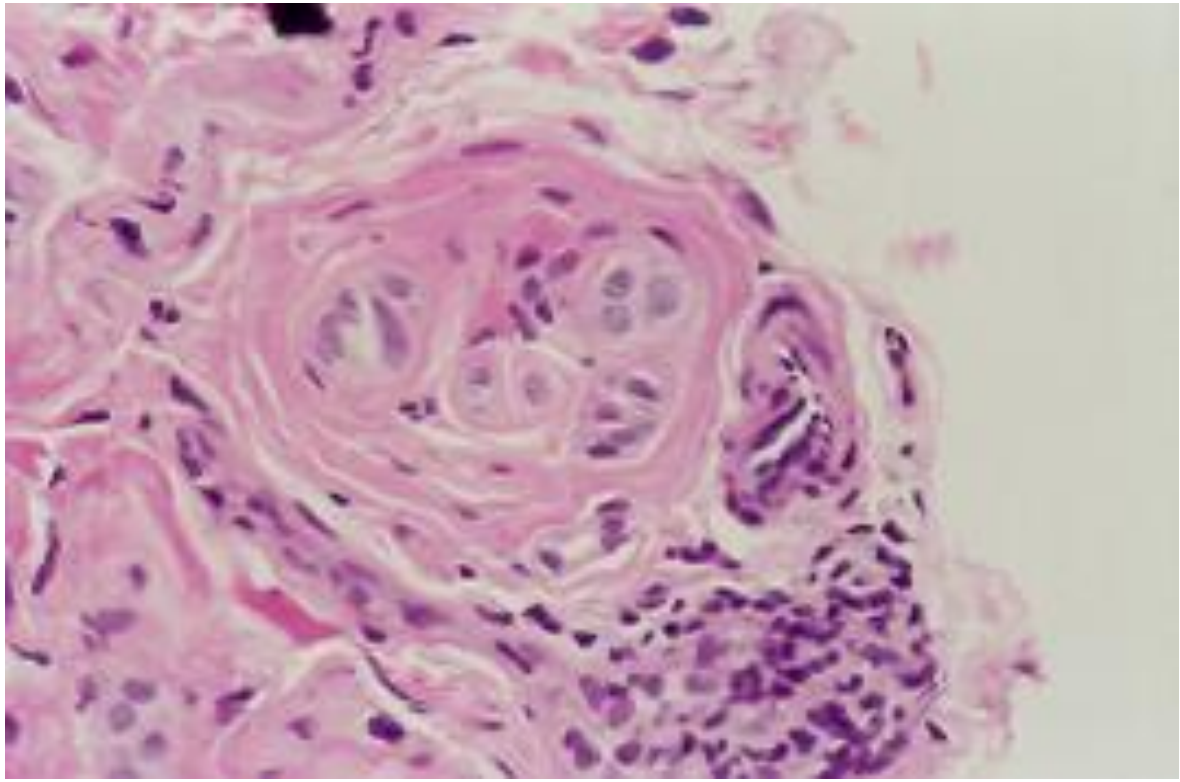
- Tumor aggregates are positive for keratin markers **CK5/6, CK903, Cam 5.2**, and **CK116**.
- **EMA and CEA** are positive with preference for tumor cells and ductal epithelium
- Positive staining with **CEA** supports adnexal origin as it is typically negative in SCC
- **p63** positivity plus **CK5/6** supports primary cutaneous origin (vs metastatic adenocarcinoma to skin)





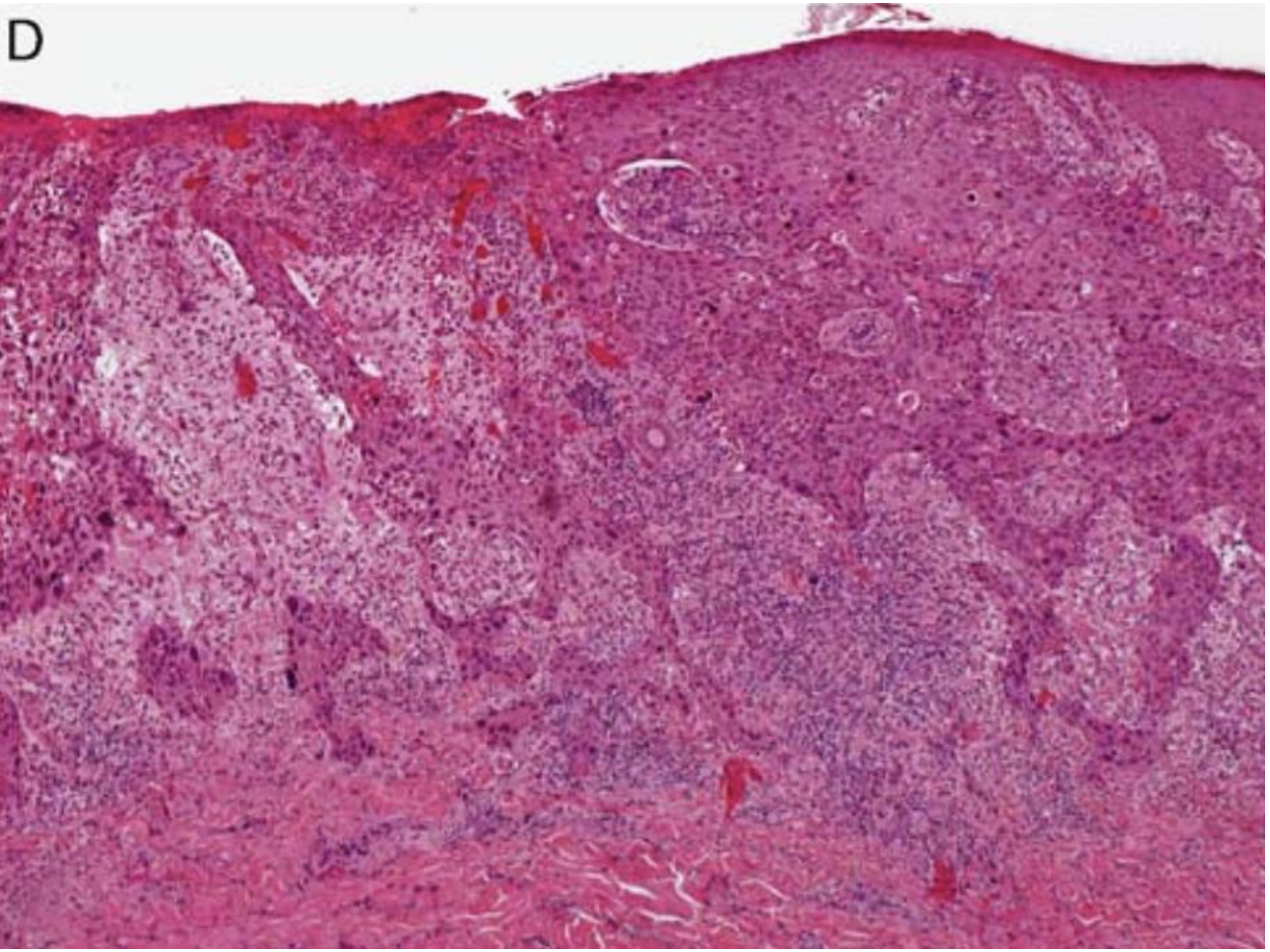
Gordon S et al. Microcystic adnexal carcinoma. Review of the Literature. Dermatol Surg 2017;43:1012–1016

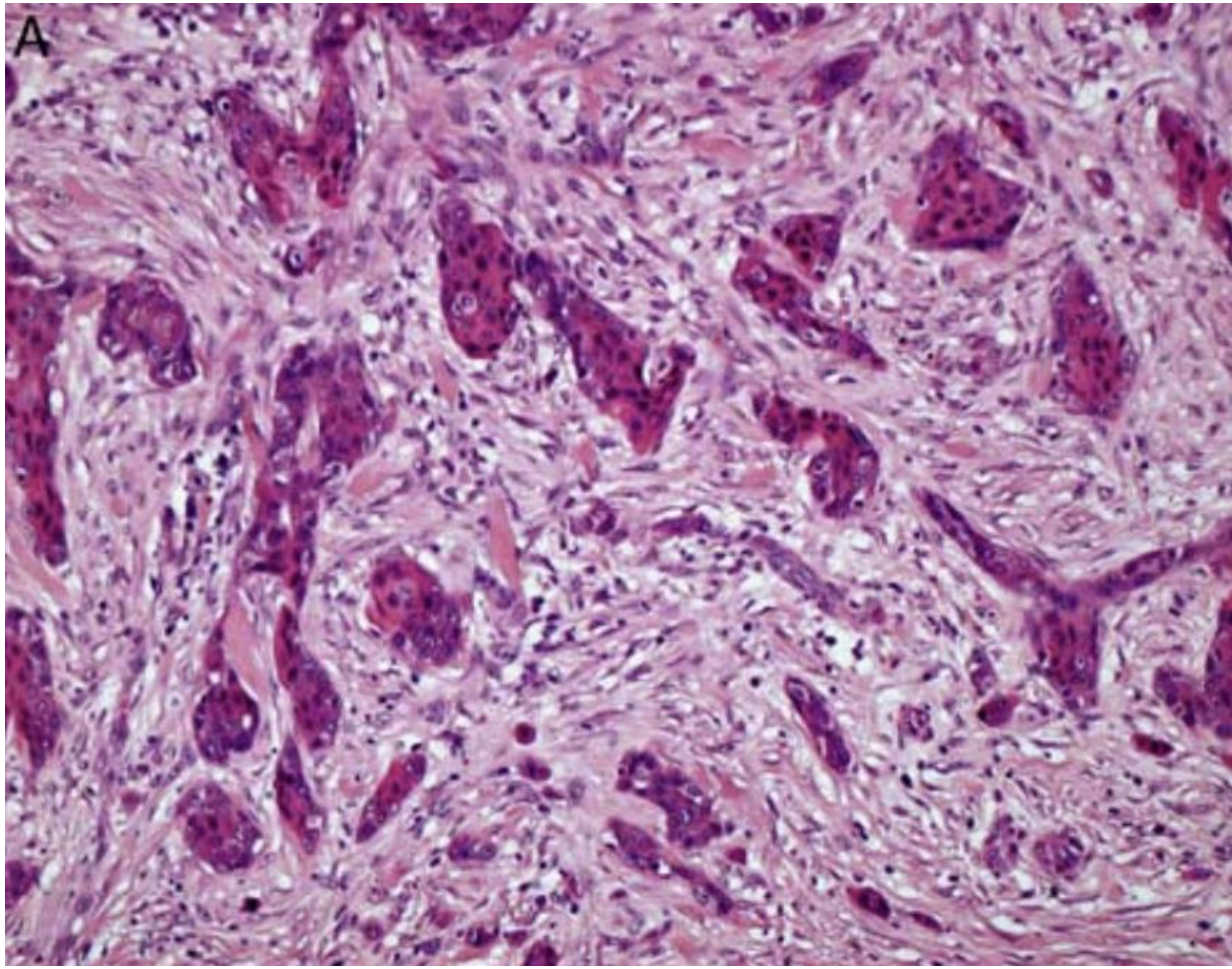




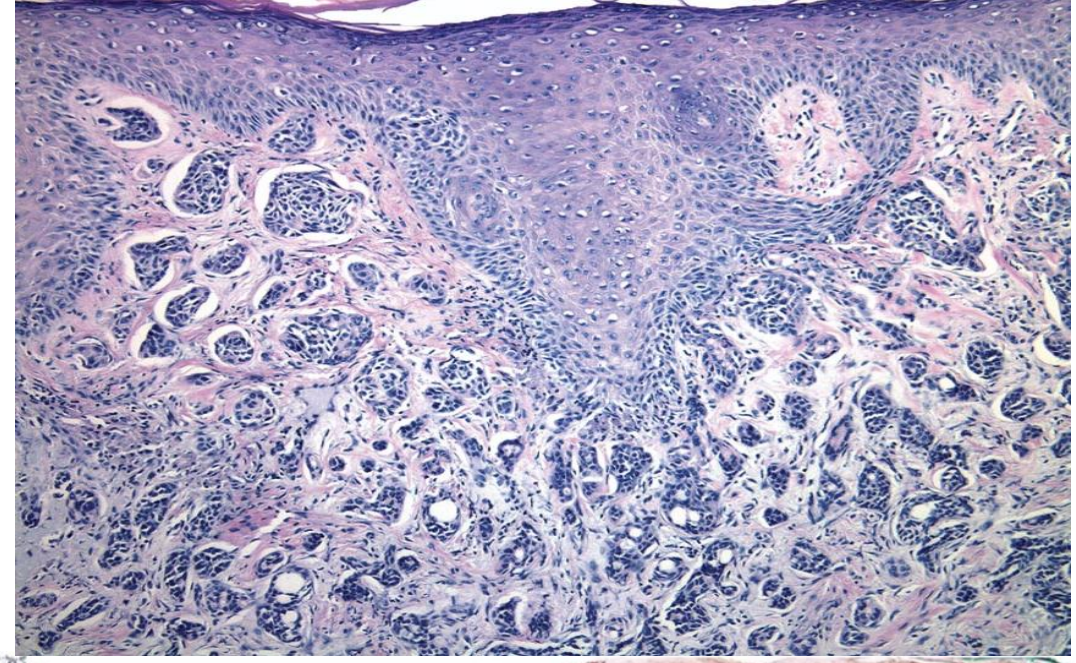
MAC with perineural and intraneural involvement

SEDC Histology

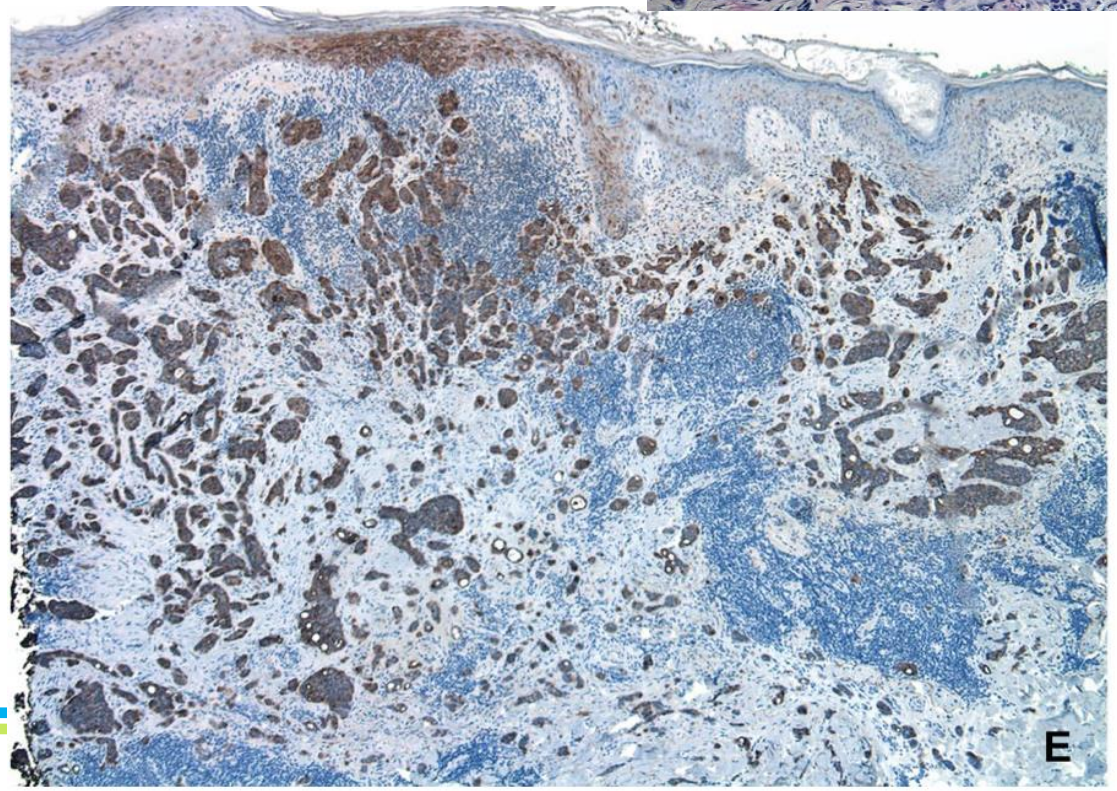


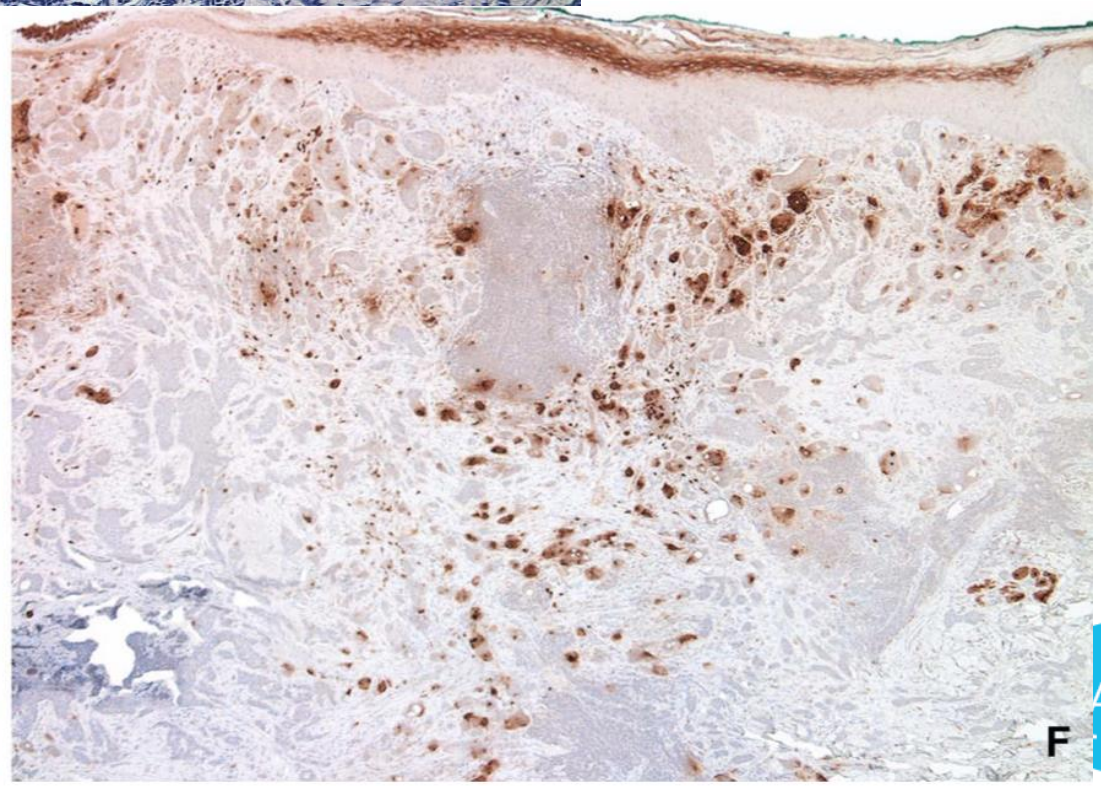


Van der Horst, Michiel PJ, et al. "Squamoid eccrine ductal carcinoma." The American Journal of Surgical Pathology 40.6 (2016): 755-760.



EMA





CEA

Shayan Cheraghlou, Nicole A. Doudican, Maressa C. Criscito, Mary L. Stevenson, John A. Carucci. **Evaluating Rates of Positive Margins After Standard Excision of Cutaneous Adnexal Malignancies. Dermatol Surg 2023;49:907–913.**

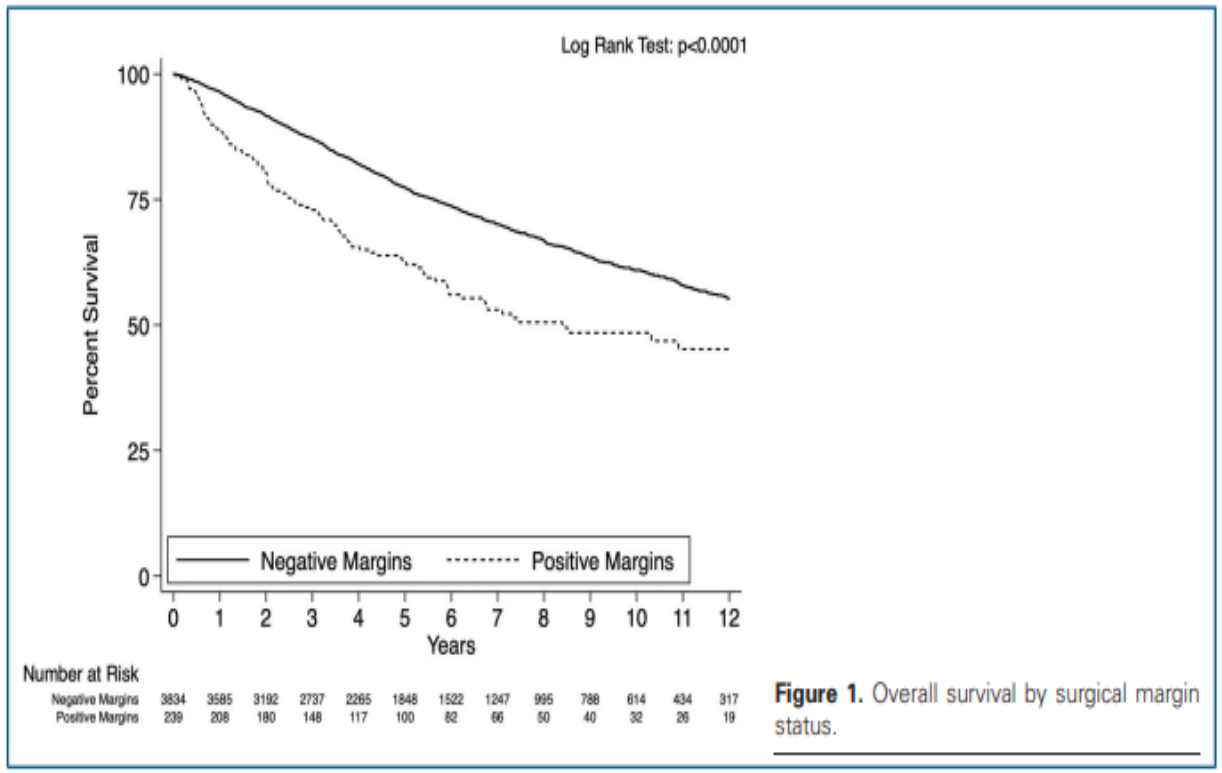
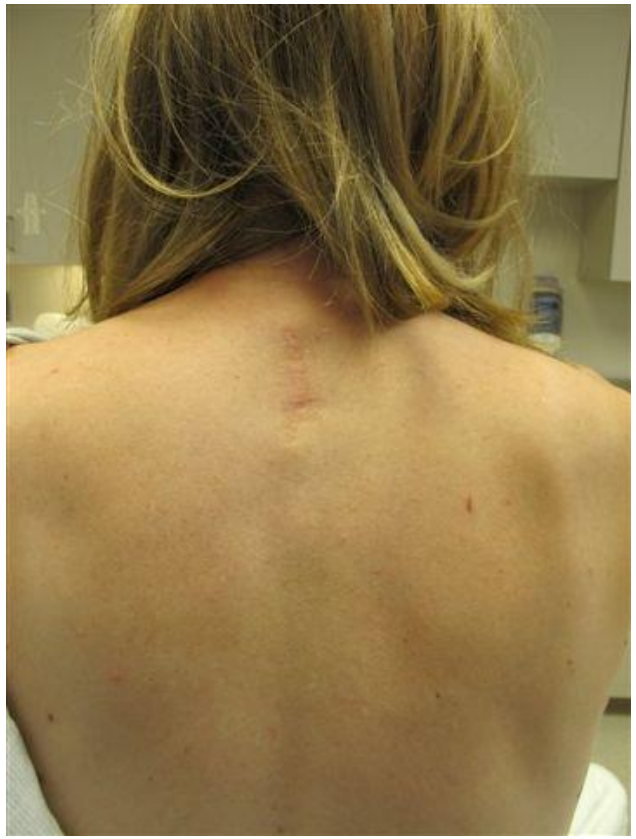
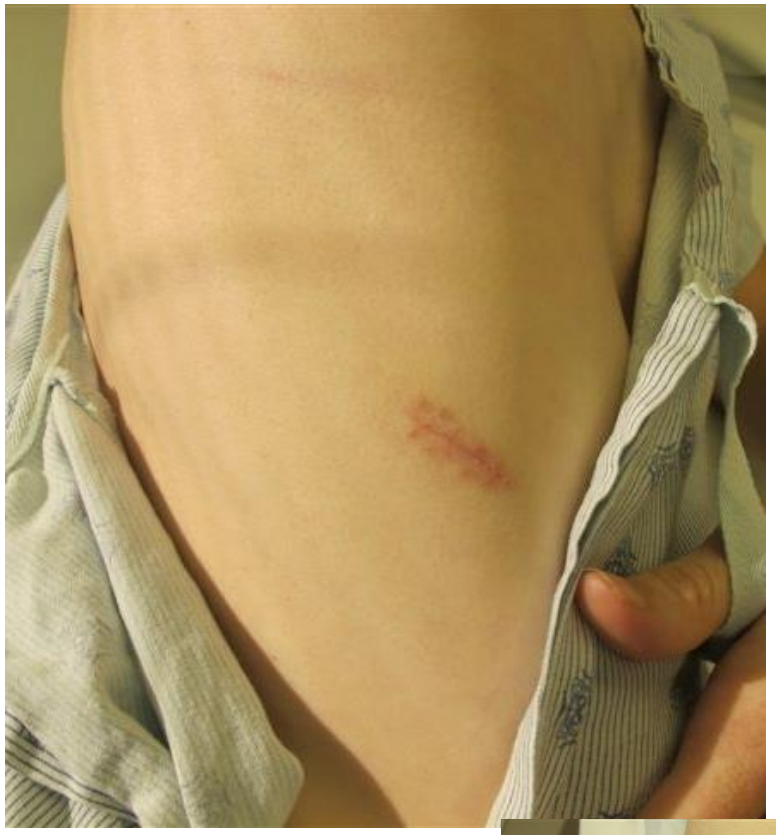


Figure 1. Overall survival by surgical margin status.

- National Cancer Database 2004-2019
- 4402 adnexal carcinomas treated with WLE vs NLE
- Tumors on HN were 2x more likely than HN tumors to have positive margins
  - Eccrine adenocarcinoma HN 12.1%
  - MAC T&E 8.0%, HN 11.6%
  - **Positive margins associated with poorer overall survival on multivariable survival analysis**
- Adnexal carcinomas on HN and some on T&E should be preferentially excised with MMS

8/2008



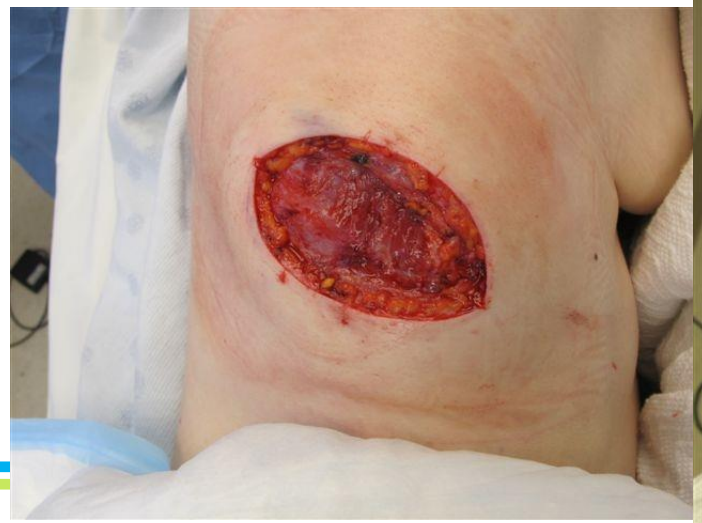


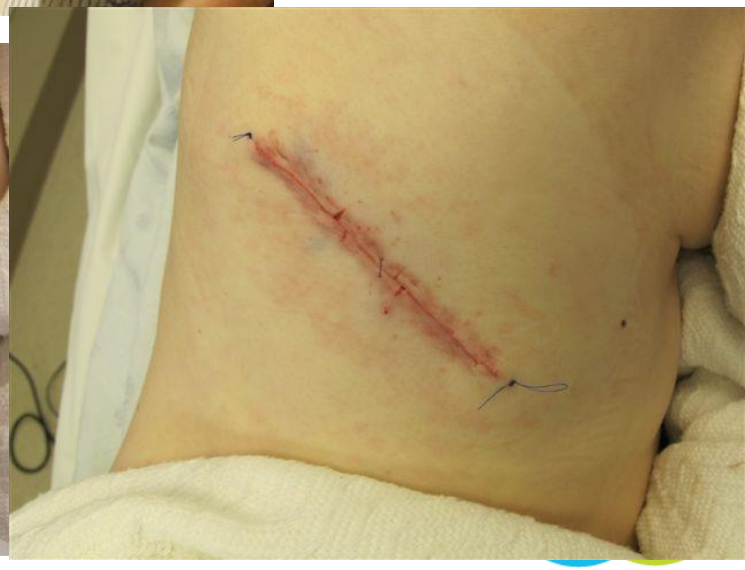
9/2010

Dermatol Surg. 2012 Nov;38(11):1876-8. doi: 10.1111/j.1524-4725.2012.02519.x. Epub 2012 Jul 17.

Two primary dermatofibrosarcoma protuberans associated with different pregnancies in a single patient.

Anderson KA, Vidimos AT.





DFSP and Pregnancy

- Dermatofibrosarcoma protuberans: report of a case with a variant ring chromosome and metastases following pregnancy. J Cutan Pathol 2006; 33: 383-388.
- Accelerated growth of dermatofibrosarcoma protuberans during pregnancy. J Amer Acad Dermatol 1999; 41: 778-83.
  - PR expression in 3 DFSP in pregnant patients, and DFSP from 2 men and 2 nonpregnant women
  - DFSP have greater expression of PDGF receptors
  - Increased levels of PDGF and progesterone in pregnancy

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Dermatofibrosarcoma Protuberans

NCCN Guidelines Index
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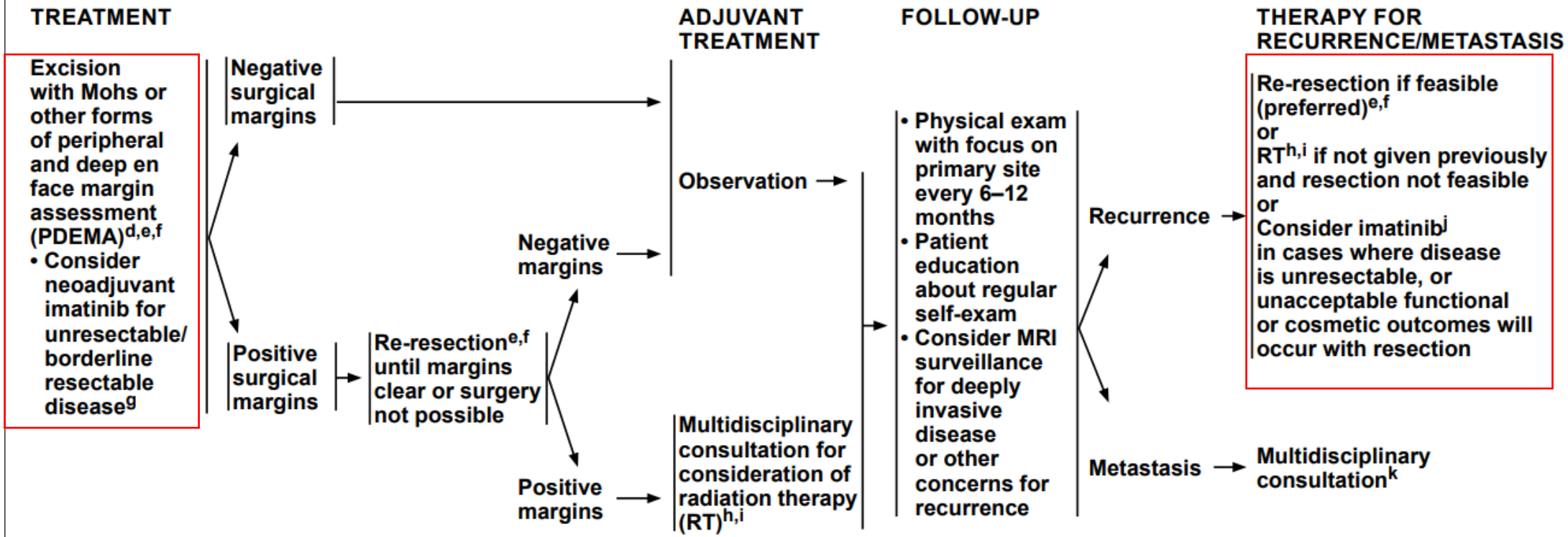
Discussion



[d] If areas of transformation to fibrosarcoma or other sarcoma subtypes are identified, multidisciplinary consultation for consideration of further treatment and surveillance is recommended. FS-DFSP is associated with a metastasis risk of 15%–20%. See the NCCN Guidelines for Soft Tissue Sarcoma for multimodal therapy and surveillance considerations including CT of draining nodal basin and chest.

[e] The most commonly used form of PDEMA is Mohs. See NCCN Guidelines for Squamous Cell Skin Cancer - Principles of PDEMA Technique. When anatomic structures at the deep margin (eg, major vessels, nerves, bone) preclude complete histologic evaluation of the marginal surface via Mohs or other forms of PDEMA, Mohs or other forms of PDEMA

[f] If PDEMA is unavailable, consider wide excision. Wide undermining is discouraged prior to confirmation of clear margins due to the difficulty of interpreting subsequent re-excised margins, and the risk of concealing residual tumor below mobilized tissue. See Principles of Excision (DFSP-B).

[g] Consider neoadjuvant imatinib for patients in whom resection with negative margins may result in unacceptable functional or cosmetic outcomes. Ugurel S, et al. Clin Cancer Res 2014;20:499-510.

[h] See Principles of Radiation Therapy (DFSP-C).

[i] When Mohs or other forms of PDEMA are utilized and margins are negative, RT is not recommended. When Mohs or other forms of PDEMA are not utilized, consider RT if margins are considered narrow by the treating physicians. RT can be considered for