2018 Park City AP Update

Appendiceal GCC and LAMN

Navigating the Alphabet Soup in the Appendix

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Appendiceal tumors

Low grade appendiceal mucinous neoplasm

- Peritoneal spread, chemotherapy
- But not called 'adenocarcinoma'

Goblet cell carcinoid

- Not a neuroendocrine tumor
- Staged and treated like adenocarcinoma
- But called 'carcinoid'

Outline

- Appendiceal LAMN
- Peritoneal involvement by mucinous neoplasms
- Goblet cell carcinoid
  - -Terminology
  - -Grading and staging
  - -Important elements for reporting

LAMN

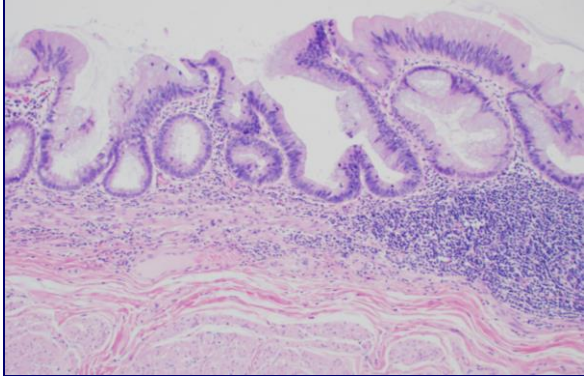
WHO 2010: Low grade carcinoma

- **Low grade**
- **'Pushing invasion'**

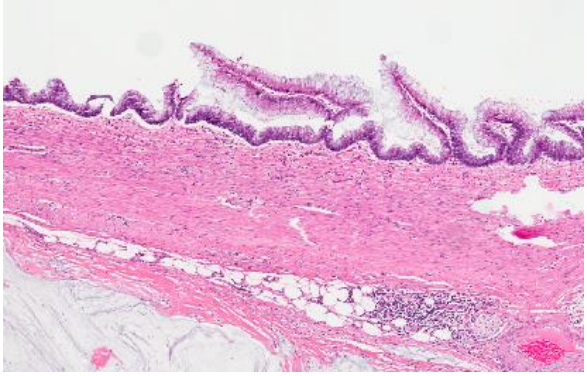
LAMN vs. adenoma

LAMN	Appendiceal adenoma
Low grade cytologic atypia	Low grade cytologic atypia
At minimum, muscularis mucosa is obliterated	Muscularis mucosa is intact
Can extend through the wall	Confined to lumen

Appendiceal adenoma: intact muscularis mucosa



LAMN: Pushing invasion, obliteration of m mucosa

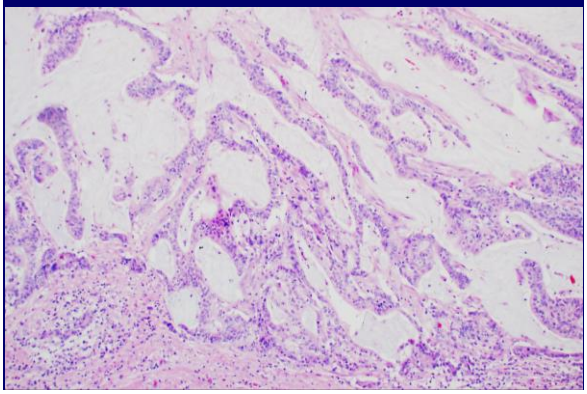


LAMN vs adenocarcinoma

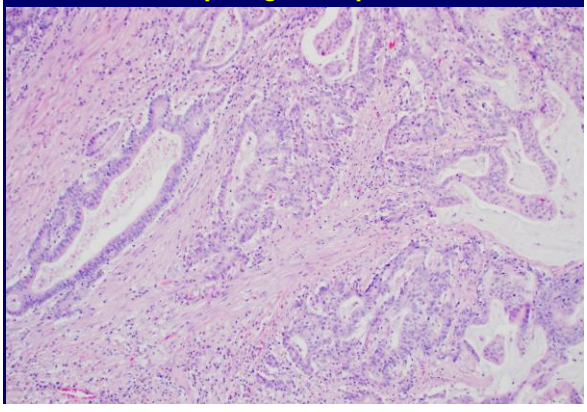
LAMN	Mucinous adenocarcinoma
Low grade	High grade
Pushing invasion -No desmoplasia or destructive invasion	**Destructive invasion** -Complex growth pattern -Angulated infiltrative glands or single cells -Desmoplasia -Tumor cells floating in mucin

WHO 2010
Davison, Mod Pathol 2014
Carr, AJSP 2016

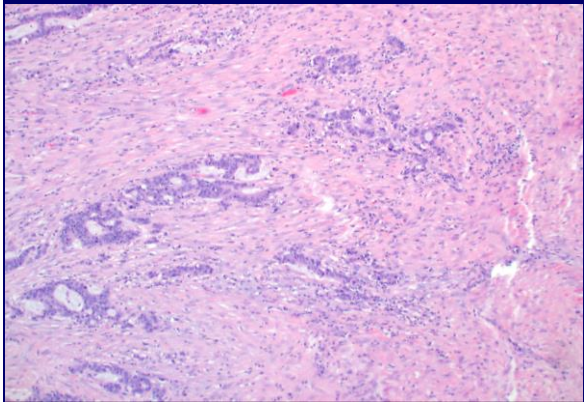
Complex growth pattern



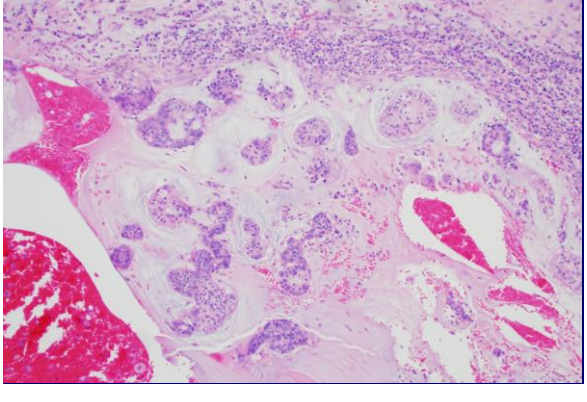
Complex growth pattern



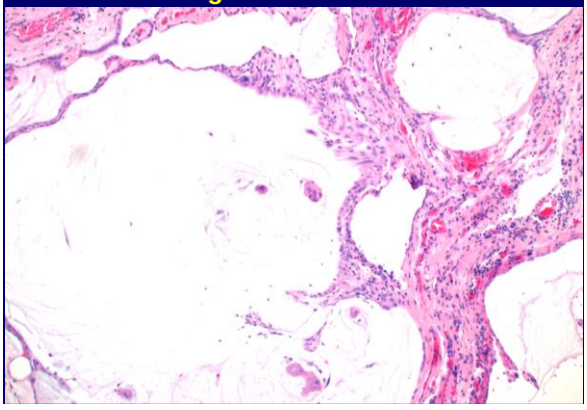
Angulated infiltrative glands, desmoplasia



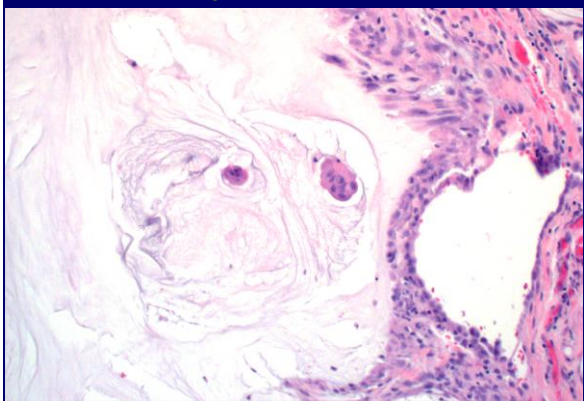
Tumor cells in extracellular mucin



Few floating cells common in LAMN



Few floating cells common in LAMN



Implications of diagnosis

	LAMN	Mucinous adenocarcinoma
LN metastasis	Rare	Common
Hematogenous spread	Rare	Can occur
Peritoneal metastasis	Common	Common
Treatment	Follow-up imaging	-Rt hemicolectomy -Systemic chemo if needed

Grade

- By definition, LAMN is low grade
- Focal or diffuse high grade changes in tumors which architecturally resemble LAMN
  - -No destructive invasion or desmoplasia

High grade appendiceal mucinous neoplasm (HAMN)

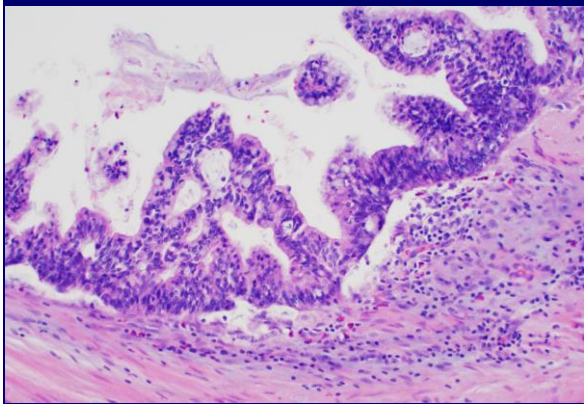
- HAMN is not part of WHO 2010 classification
- Included: AJCC 8th edition
  CAP protocol (2018 version)

Carr, AJSP 2016: Peritoneal Surface Oncology Group International (PSOGI)

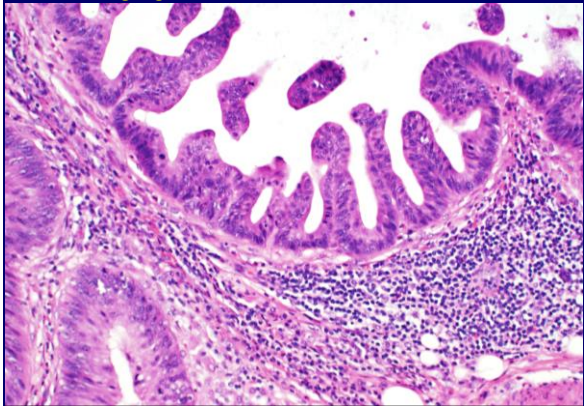
HAMN: rare tumor

- Architecture like LAMN, no destructive invasion or desmoplasia
- Focal or diffuse high grade cytologic atypia

High grade features: cribriform growth pattern



HAMN: high grade features, no destructive invasion



LAMN: staging

- WHO 2010: Low grade carcinoma
- AJCC and CAP:
  LAMN should be staged

LAMN: staging challenges

- Erroneous interpretation as mucinous adenocarcinoma
- T category is difficult to apply
  Depth of cellular or acellular mucin

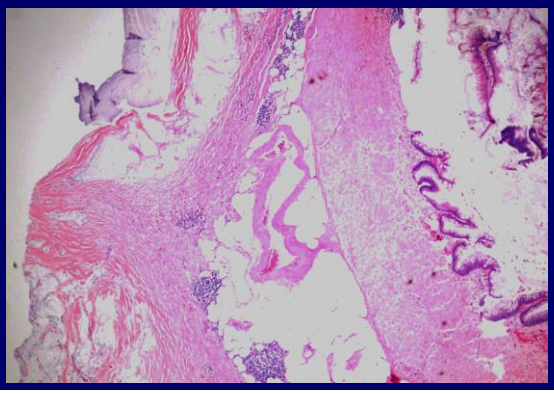
LAMN: depth of invasion and recurrence

Study	Confined to MP	Acellular mucin beyond MP	Cellular LAMN beyond MP
Umetsu/Kakar 2016	0/21	0/5	4/7
Higa 1973		0/7	4/7
Misdraji 2003	0/27	*	20/31
Pai 2009	0/16	1/14	21/27
Yantiss 2009	-	1/44**	2/10
Total	0/64	2/70 (3%)	51/82 (62%)

LAMN staging: AJCC 8th edition

Category	Change/update
Tis (LAMN)	LAMN extending into muscularis propria, but not beyond it
T1, T2	Not applicable to LAMN
T3	Cellular LAMN into subserosa *?Acellular mucin into subserosa*
T4a	Involvement of serosal surface Cellular LAMN or acellular mucin

LAMN: Acellular mucin on serosal surface



LAMN: Acellular mucin as T4a

- Based on limited data
- Risk of overtreatment
- Pathology report:

"Acellular mucin on serosal surface has a very low risk of recurrence, and categorization of this finding as T4a is based on limited data."

LAMN

Elements in pathology reporting

- Submit the entire appendix
- Extent of disease: both cellular and acellular mucin (T category)
- Margin assessment
- Absence of high risk features:
  - No high grade cytology or complex growth
  - No destructive invasion or desmoplasia

LAMN

Do not use obsolete terms

- Mucocele
- Mucinous cystadenoma

HAMN

Elements in pathology reporting

- Extent of high grade changes
- Use mucinous adenocarcinoma staging scheme
  - -Outcome may be similar to mucinous AC?

AJCC, 8th Edition
Misdraji, AJSP 2003

Peritoneal involvement

- Terminology
- Grading
- Treatment

Pseudomyxoma peritonei

- Mucinous ascites
- Omental cake
- Mucin accumulation in peritoneum due to involvement by mucinous neoplasm

Peritoneal involvement

Pseudomyxoma peritonei

Low grade	High grade
LAMN with peritoneal involvement, or Mucinous adenocarcinoma, low grade with peritoneal involvement	Mucinous adenocarcinoma, high grade with peritoneal involvement
Mucinous carcinoma peritonei, low grade	Mucinous carcinoma peritonei, high grade
Disseminated peritoneal adenomucinosis (DPAM)	Peritoneal mucinous adenocarcinoma (PMAC)

Peritoneal involvement

Low grade
LAMN with peritoneal involvement
Mucinous adenocarcinoma, low grade with peritoneal involvement
Mucinous carcinoma peritonei, low grade
Disseminated peritoneal adenomucinosis (DPAM)

Appendix shows LAMN

- LAMN with peritoneal involvement
- Include synonyms in a comment

Appendix: no LAMN or not known

- Mucinous carcinoma peritonei, low grade
- Mucinous adenocarcinoma, low grade

Peritoneal involvement

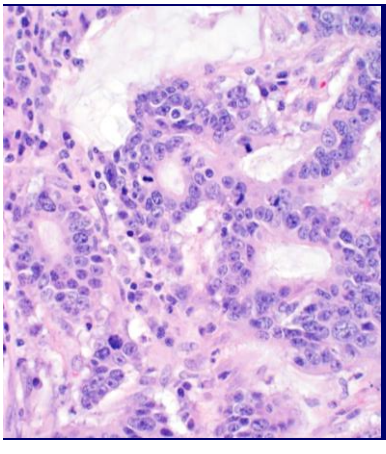
High grade
Mucinous adenocarcinoma, high grade with peritoneal involvement
Mucinous carcinoma peritonei, high grade
Peritoneal mucinous adenocarcinoma (PMAC)

Primary sites

- Appendix
- Colorectum
- Ovary
- Pancreas

Grading of peritoneal disease

WHO 2010
2-tier scheme -Low grade -High grade
Criteria -Cytologic atypia -Architecture



High grade

-Complex growth
-Stratification
-Loss of polarity
-Prominent nucleoli
-Frequent mitoses
-Signet ring cells

Grading of peritoneal disease

WHO 2010	AJCC 7th edition/CAP
2-tier scheme -Low grade -High grade	3-tier scheme -Well-differentiated (G1) -Moderately differentiated (G2) -Poorly differentiated (G3)
Criteria -Cytologic atypia -Architecture	No defined criteria -Extent of gland formation not applicable to mucinous tumors

Study	# of cases	Grading scheme	5-year survival
Ronnett (2001)	109	DPAM PMCA-I/D PMCA	75% 50% 14%
Smeenk (2007)	103	DPAM PMCA-I PMCA	75% 42% 0%
Guo (2012)	92	DPAM PMCA-I/D PMCA	80% 67% 50%
Shetty (2013)	211	PMP1 PMP2 PMP3	86% 63% 32%
Davison (2014)	151	G1 G2 G3	91% 61% 23%
NCDB database	3105	Well differentiated Moderately differentiated Poorly differentiated	57% 32% 11%

Gestalt grading scheme

- **Looks good: G1**
- **Looks bad: G3**
- **All others: G2**

AJCC 8th edition/CAP
(modified Davison scheme)

G1	**-Low grade cytologic atypia (similar to LAMN)** **-Includes acellular mucin** **-Cellularity <20%** **-No destructive invasion of implants**
G2	-Mix of low and high grade cytologic atypia, or diffuse high grade cytologic atypia -Architectural complexity -Destructive invasion of implants -Cellularity >20%
G3	-Signet ring cells infiltrating the stroma -Poorly differentiated adenocarcinoma component

Davison, Mod Pathol 2014

AJCC 8th edition/CAP
(modified Davison scheme)

Grading parameters

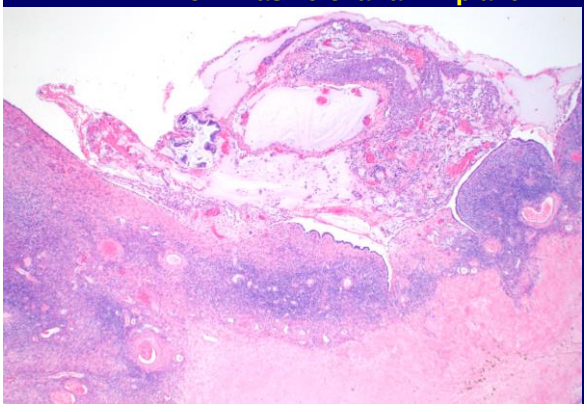
- **Cytoarchitectural atypia**
- **Cellularity**
- **Invasive implants**
- **Signet ring cells**

Davison, Mod Pathol 2014

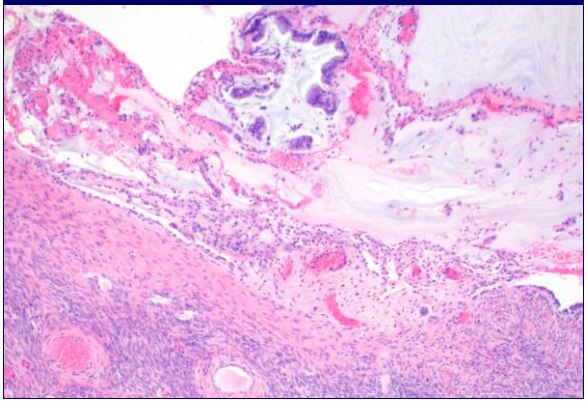
Invasive implants

- **Mucinous tumors on visceral organs like liver, colon etc. not sufficient**
- **Destructive invasion and desmoplasia**

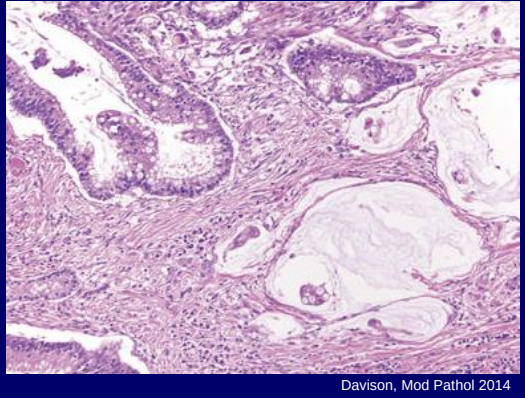
LAMN: Noninvasive ovarian implant



LAMN: Noninvasive ovarian implant

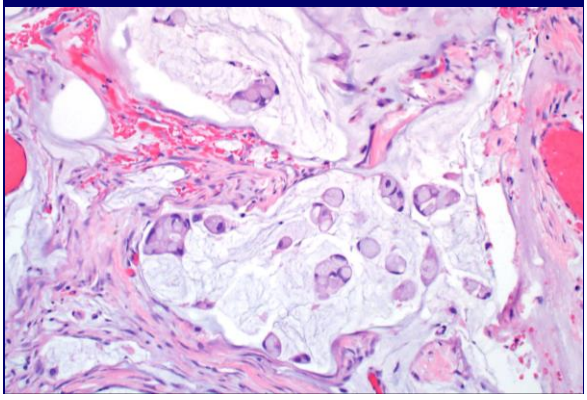


LAMN: Invasive implant

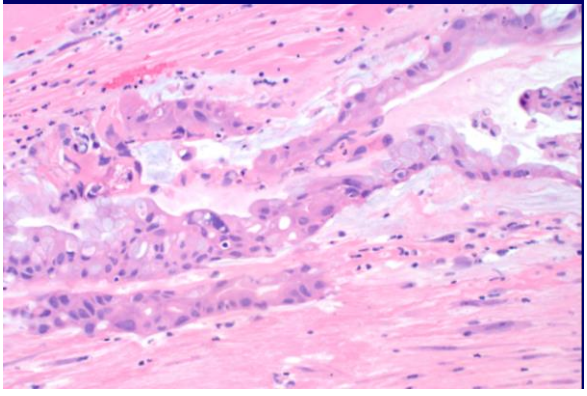


Davison, Mod Pathol 2014

Peritoneum: signet ring cell carcinoma



Pseudo-signet ring cells



Signet ring cells in grading

- >10% cutoff has been suggested for G3 designation (not specified in AJCC)
- Disregard cells in mucin resembling signet ring cells
- Consider only if infiltrating signet ring cells in stroma

Sirintrapun, Hum Pathol 2014
Davison, Mod Pathol 2014

Challenges in grading

- Invasive implants
- Signet ring cells
- Small or borderline G2 component
- Discrepant grading in appendix and peritoneum

Challenges in grading

Small or borderline G2 component

- Significance unclear
- Descriptive report stating that there is a minor G2 component

Challenges in grading

Discrepant grade in appendix and peritoneum

- Uncommon
- Higher grade peritoneal disease generally drives prognosis

AJCC 8th: M categories

Category	Definition
M1a	Acellular mucin with disseminated peritoneal involvement
M1b	Peritoneal mucinous depositis containing tumor cells
M1c	Metastasis to sites other than peritoneum

Stage	Definition
IVa	Any T or N, M1a (acellular mucin) Any T or N, M1b (G1)
IVb	Any T or N, M1b (G2, G3)
IVc	Any T or N, M1c (Any G)

Grade: impact on treatment

Stage IVa M1a: acellular mucin M1b : G1 tumors	Stage IVb M1b: G2, G3 tumors
Combined peritoneal surgery (tumor debulking) with HIPEC (hyperthermic intraperitoneal chemotherapy)	Role of surgery and HIPEC controversial
Systemic chemotherapy not useful	Systemic chemotherapy

HIPEC: Hot chemotherapy leads to hot debate

Debate at ASCO meeting

- **'Heating drugs makes them more effective'**
- **'Precious little data that heated chemotherapy does anything'**

LAMN Tis with peritoneal disease

- LAMN confined to muscularis propria (Tis) but with peritoneal disease
- TisN0M1: does not make sense
- Explanations:
  - Not entirely submitted
  - Defect has 'sealed'
- Suggestion: pTxN0M1

Peritoneal involvement: summary

- Use appropriate terminology
- Include synonymous terms in report
- Use 3-tier grading scheme (AJCC 8th edition)
- Uncommon situations
  - Grade discrepancy: appendix and peritoneum
  - Minor component of higher grade

Goblet cell carcinoid

- Terminology
- Grading and staging
- Important elements for reporting

Terminology

- Pure GCC
- GCC with adenocarcinoma
- GCC with well-differentiated neuroendocrine tumor

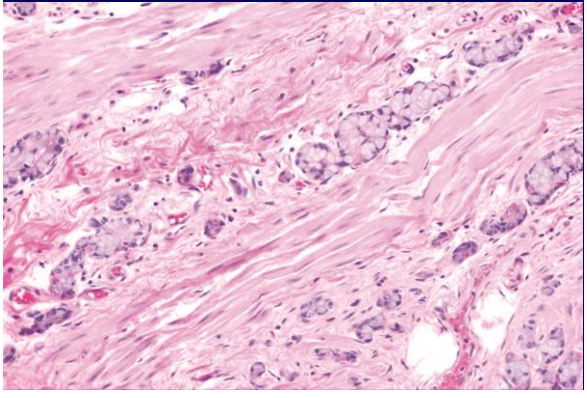
Goblet cell carcinoid

- Primarily in appendix
- Rare reports: colon, ampulla

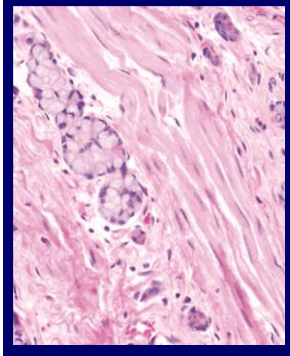
Unique features

- Recapitulates the crypts (crypt cell adenocarcinoma)
- Dual features
  - Exocrine: goblet cells, mucin
  - Endocrine: NET-like areas, IHC, EM

Pure goblet cell carcinoid

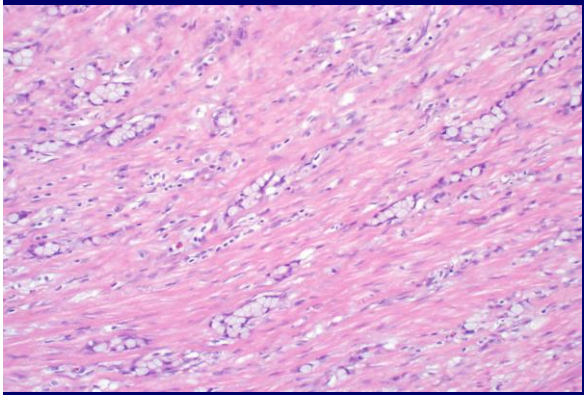


Pure goblet cell carcinoid

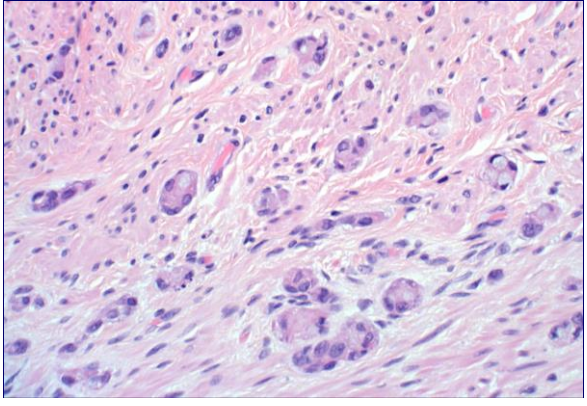


- Crypt-like clusters of ‘goblet cells’
- No large irregular clusters or sheets
- Cytologic atypia mild
- Mitoses rare
- No desmoplasia or destructive invasion

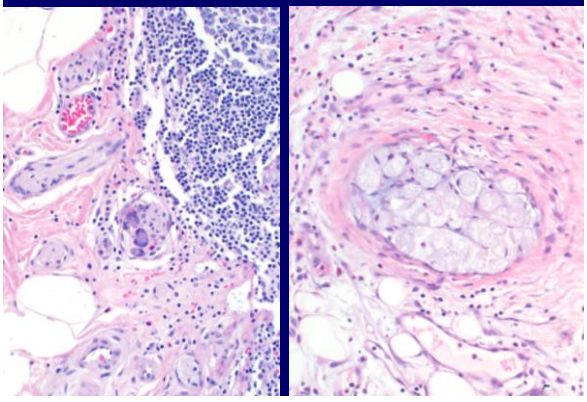
GCC: single filing in muscularis propria



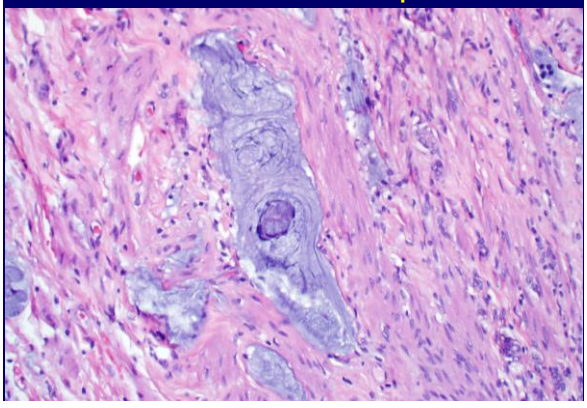
GCC: small tubules with minimal atypia



GCC: perineural and vascular invasion



GCC: extracellular mucin pools



GCC with adenocarcinoma

Variety of terms

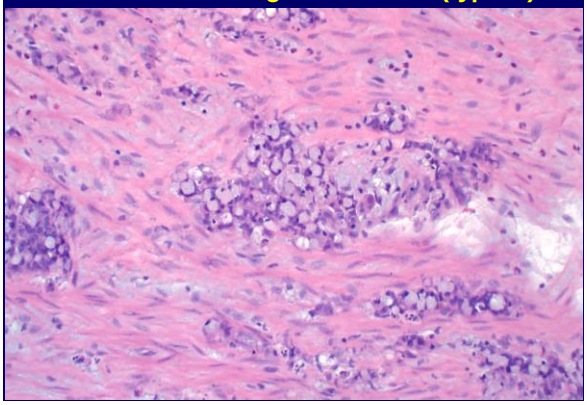
- Adenocarcinoma ex GCC (Tang scheme)
- Mixed GCC-adenocarcinoma
- Crypt cell adenocarcinoma

GCC with adenocarcinoma

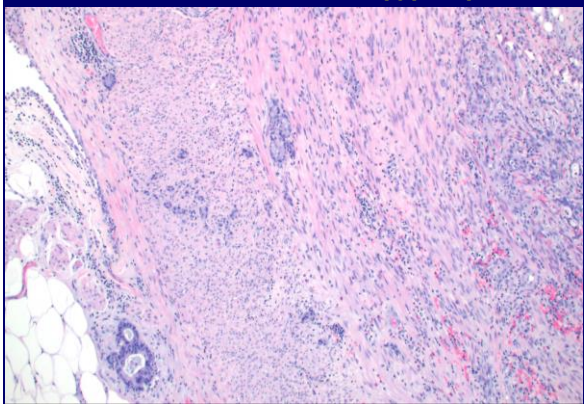
- Type A: Pure GCC
- Adenocarcinoma ex GCC, type B
  - -Loss of cohesive groups
  - -Large irregular clusters
  - -More cytologic atypia
- Adencoarcinoma ex GCC, type C
  - - Poorly differentiated
  - -Diffuse dingle cells or sheets of signet ring cells

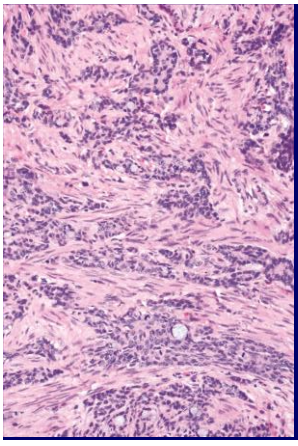
Tang, AJSP 2008

GCC with AC: irregular clusters (type B)

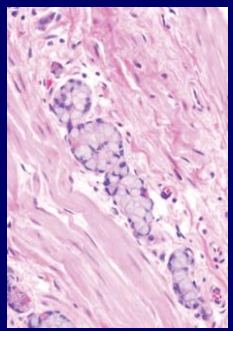


GCC with well-diff AC (type B)





GCC with poorly-diff adenocarcinoma (type C)



Terminology

- Goblet cell carcinoid
- Mixed GCC-adenocarcinoma
  - -Proportion of adenocarcinoma
    - <25%, 25-50%, >50%
  - -Subtype and differentiation

Taggart, Arch Path Lab Med 2013
Wen/Kakar, Hum Pathol 2017

Clinical impact

Pure GCC vs. mixed GCC-AC

- GCC-adenocarcinoma have worse outcome, treatment largely similar
- Rt. hemicolectomy
  - ?GCC limited to submucosa
- Adjuvant chemotherapy especially if LN+ or peritoneal spread
- Possible prophylactic oophrectomy

Mixed GCC-adenocarcinoma

- **WHO 2010 recommended term 'mixed adenoneuroendocrine carcinoma' should not be used**
- **Can be misinterpreted as neuroendocrine carcinoma (NEC)**
- **Platinum-based chemotherapy used in NEC, but not in GCC**

Common errors

Incorrect interpretation	Number
NET staging scheme should be used for GCC	41%
Ki-67 necessary for grading	43%
Oncologists interpreted mixed GCC-AC as poorly differentiated NEC	2 cases

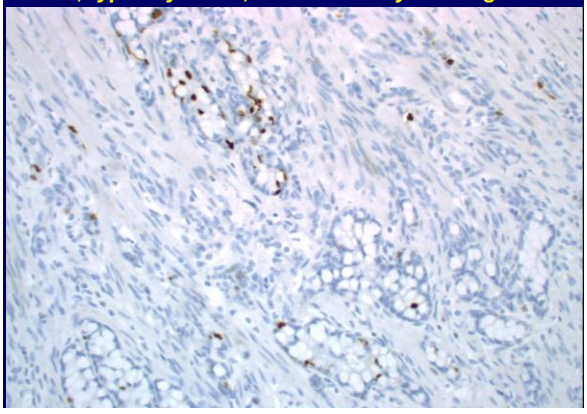
Wen/Kakar, Hum Pathol (in press)

Goblet cell carcinoid

- **GCC: pattern of spread like an adenocarcinoma**
- **Genetic changes**
  - **No *KRAS* mutation**
  - **p53, APC mutation rare**
  - **Mutations in chromatin remodeling genes**

Wen/Kakar, USCAP 2017

Ki67, typically <20%, not necessary for diagnosis

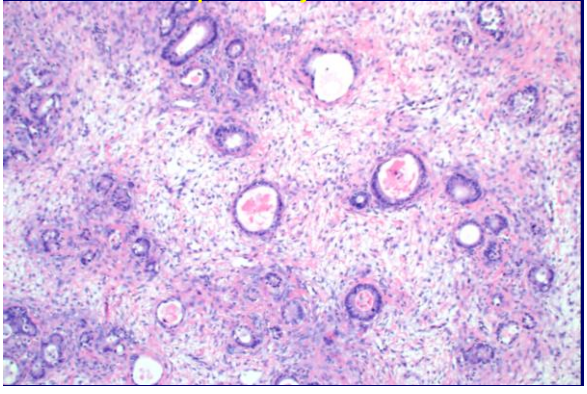


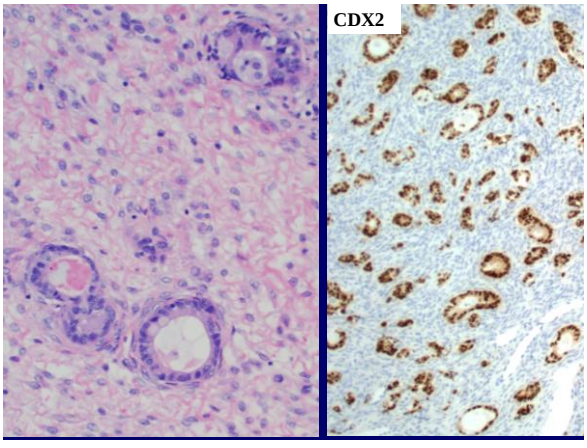
Terminology

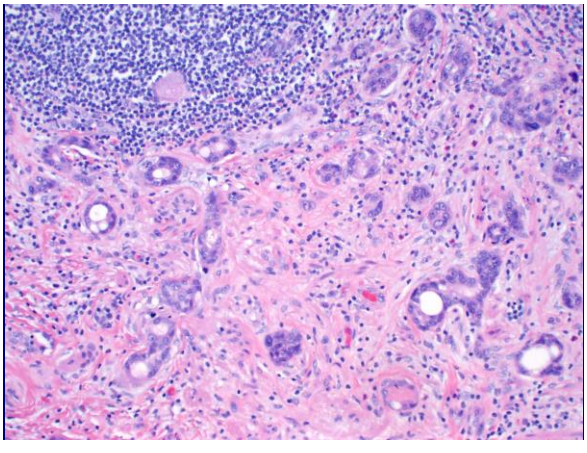
Next WHO (if I were to write it)

- Goblet cell carcinoma (GCC)
- Grading scheme
  - Grade 1: Pure GCC
  - Grade 2: GCC with atypia or areas with well to moderately differentiated adenocarcinoma
  - Grade 3: GCC with signet ring cell carcinoma or poorly differentiated adenocarcinoma

48/F with history of colon adenocarcinoma in polyp
Oophrectomy for tumor







GCC: summary

- Use appropriate terminology
- Comment
  - -State that this is not a NET or NEC
  - -Include commonly used synonyms
- Do not grade based on mitoses/Ki-67 index
- Staging scheme for adenocarcinoma, not NET
- Do not use the adenoneuroendocrine carcinoma