The trip from “observation” to clinical practice

“Logical or illogical intellectual drift?”

Early example from my first year in residency

- How many blocks of a TURP do you put in?
  - 6
  - Why?
  - Used to put in 5, but one day…..
  - Of an additional 5 blocks put in, the first (random) one looked at had cancer, so
  - since that time we always put in 6

Classical examples of seemingly logical illogical conclusions

- The earth is the center of the universe
- The world is flat
- Potatoes lead to crime
- Money causes breast carcinoma

When illogic doesn't seem so illogical

- Small cell undifferentiated lung carcinoma does not benefit from surgical therapy (documented)
- Small cell undifferentiated lung carcinoma marks with chromogranin (or synaptophysin) immunostains (documented)
- Therefore, these stains should be used to determine if a lung carcinoma deserved surgical therapy (undocumented)
- True or false?
- Do tumors that look like small cell undifferentiated carcinoma but which do not mark with neuroendocrine markers benefit from surgical therapy (no)?
- Do tumors that do not look like SCUCa but do stain with these markers benefit from surgery?

Mod Pathol 2001;14(9):880–885

Microtubule-Associated Protein-2: A New Sensitive and Specific Marker for Pulmonary Carcinoid Tumor and Small Cell Carcinoma

From the Discussion:

"Most pulmonary carcinomas may be readily classified based on their histological features. However, diagnosis and classification by routine light microscopic examination may be difficult and challenging, especially when the tumor is a poorly or undifferentiated carcinoma. *Accurate identification of small cell carcinomas in biopsies is critical, because these tumors are optimally treated by modalities other than surgeries."*

We recommend that MAP-2 be added to immunohistochemical panels to separate non-neuroendocrine from neuroendocrine lung tumors. [BTW, 16% of adenocarcinoma and 16% of squamous cell carcinomas also stained for MAP-2, "focally"].

A question to ponder:

So, would MAP-2 positivity in a biopsy of a lung tumor be enough to say "don't remove it – just give chemo and radiation", or is histology still the determining factor?

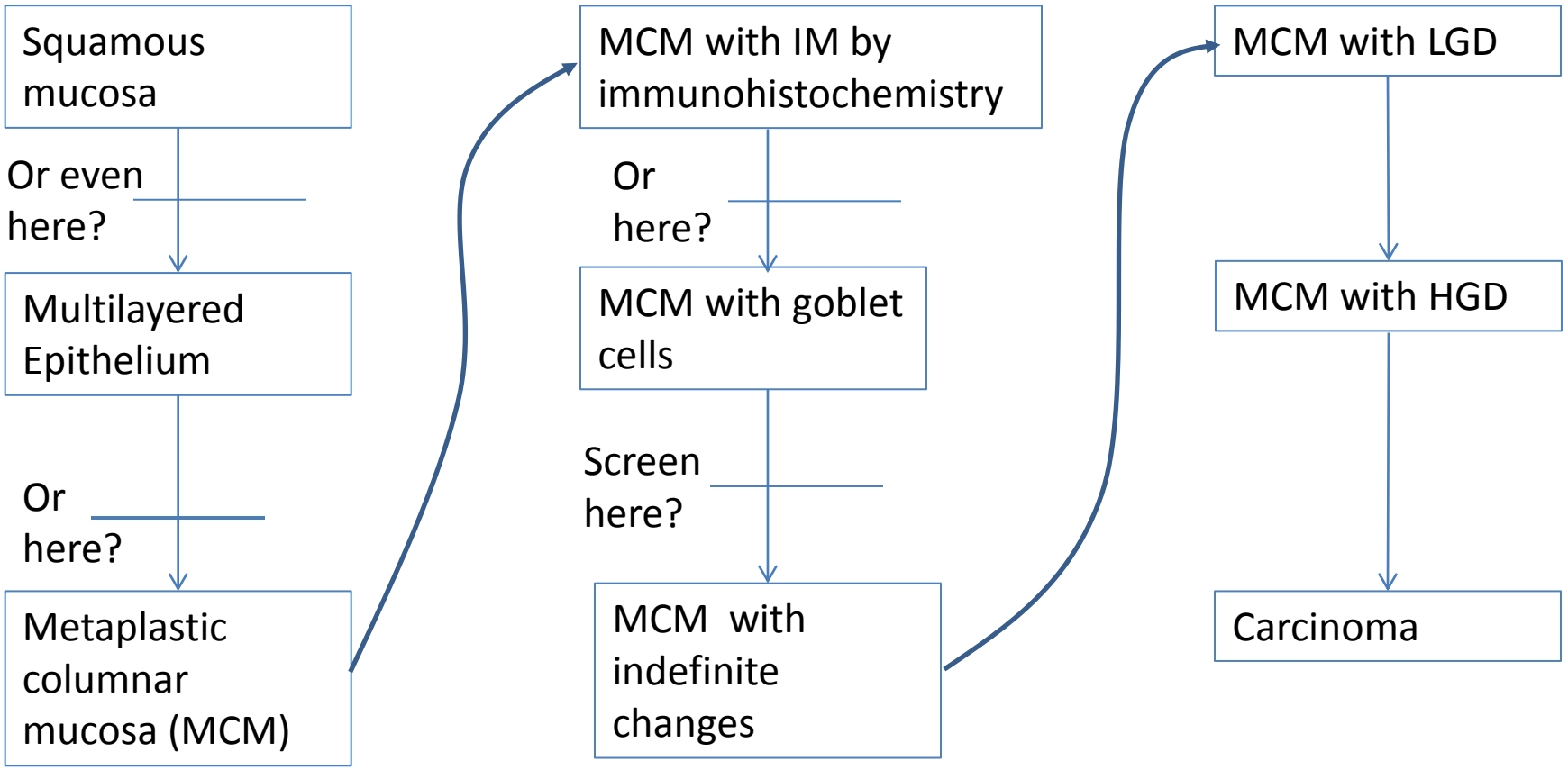
Boolean logic gone bad

- If A = B, and B = C then A must equal C.
- Works well with numbers; does it work biologically?
  - Only if B = C has 100% sensitivity and specificity (assuming, for example, that C is the immunohistochemical stain)

Problems with “associative” data

- Associations do not mean cause and effect nor do they usually mean equivalency.
- Even if there is a “cause – effect”, what is the proportion of cases with the “cause” that go on to have the “effect” (i.e. how many false positive results are there).
- Even if there is a “cause – effect” phenomenon, at what stage in development of the ultimate effect (e.g. cancer) does one want to intervene?

Multistep process to carcinoma in the esophagus – where do we intervene*?



* = “intervene” can mean start surveillance, do surgery, ablate, etc.

GI and hepatic pathology is not immune

- Some recent examples
  - Use of ubiquitin and cytokeratin 8/18 to identify “incipient” Mallory-Denk bodies and ballooning degeneration in NASH (are these changes really the functional equivalent of fully formed histological abnormalities?)
  - Use of surrogate markers (e.g. HepPar1) to identify “intestinal metaplasia” before it is identifiable histologically (does HepPar1 positivity really carry the same malignant implication as fully identifiable metaplasia?
  - Identification of many different “variants” of “dysplasia” in Barrett’s esophagus and IBD (crypt cell dysplasia, “serrated” dysplasia, incomplete goblet cell maturation) (do these carry the same clinical significance as conventional “dysplasia”).

[686] Incomplete Goblet Cell Maturation: A Distinctive Form of Flat Dysplasia in IBD.

Design: Our GI Database was queried for a diagnosis of IGCM between 1994-2010. The diagnoses were correlated with synchronous and metachronous dysplasia using chi-square statistics. IGCM was usually graded indefinite for dysplasia (IND), mainly due to the difficulty of excluding regenerative change with certainty, however, diagnoses of indefinite probably negative (IND-N) or probably positive (IND-P) were rendered when regeneration seemed more or less likely based on the inflammatory surroundings. A minority of cases were interpreted as low-grade dysplasia (LGD) or high-grade dysplasia (HGD) based on criteria for conventional dysplasia.
Results: IGCM was reported in 80 patients (51 males, 29 females, ages 22-81y). It accounted for 4.7% of all biopsies with definite or indefinite dysplasia (9% IND-N, 52% IND, 19% IND-P, 17% LGD, and 2% HGD). A significant correlation was observed between the grade of dysplasia assigned to IGCM and the presence of synchronous conventional dysplasia: no biopsies with conventional dysplasia were observed in the same procedure as IND-N compared to 29% in procedures with IGCM of grade IND or higher (p=0.008). Among 56% of patients with IGCM who had undergone previous biopsies, no significant differences were noted in the prevalence of previous dysplasia.
Among 56 IGCM patients with long-term follow-up, LGD and carcinoma were more prevalent among 48 with IGCM graded IND or higher (15 and 10, respectively) than among 8 graded IND-N (0 and 0, respectively), though statistically insignificant. Among these 56 patients, IGCM persisted in subsequent procedures in 13 (23%). Of 21 patients who had IGCM as their first and only dysplastic finding and adequate follow-up, 6 (29%) developed conventional dysplasia including 4 LGD, 1 HGD and 1 carcinoma.
Conclusions: IGCM, a distinctive type of flat dysplasia in IBD, should be considered when an unexplained absence of goblet cells is noted in the setting of IBD and ***should be managed similarly to conventional types of dysplasia***.
Category: Gastrointestinal

Monday, February 28, 2011

Evidence that “variant” dysplasia should be treated the same as “conventional” dysplasia

- “Variant” dysplasia is associated with simultaneous conventional dysplasia or with subsequent development of conventional dysplasia or rarely carcinoma.
  - This is never a one-to-one association
- Little evidence, however, that identification of “variant” dysplasia reduces the incidence of carcinoma or decreases mortality (nor is there much evidence for this with conventional LGD).

If using “conventional LGD” as a justification for “variant” dysplasia we must remember

- Reproducibility of the diagnosis of LGD is fair at best
- Reproducibility of “variant” dysplasia is not know to be any better and
- The association of LGD with subsequent carcinoma development is less than perfect by far.
- (so, is the association of variant dysplasia any different than that of “indefinite for dysplasia”?)

What would it take to have “proof” of significance for “variant” dysplasia?

- Ideally, a prospective, randomized trial (i.e. 50% of patients with dysplasia undergo colectomy, 50% don’t, follow-up to see how many in each group eventually die of cancer), which is not going to occur.
- Next best, a prospective comparison of patients with variant dysplasia alone versus no dysplasia, IND and LGD with follow-up to see how many eventually develop HGD or carcinoma.
  - This would not address the effectiveness of the identification of VD for preventing death due to carcinoma, only its equivalency to LGD or whatever other comparative marker you are using.
  - The study cannot be done if “variant” dysplasia diagnoses result in colectomy

How much proof do you need before putting something into clinical practice?

- Randomized controlled trials?
- Prospective studies?
- Retrospective analysis of case series?
- Pathological associations (pathology case observations)?
- Consensus of experts?

So, in the end what level of proof is necessary to put a theory into practice?

- Which should bring us to our panel discussion


THE END
Thank you for your attention and have a great day!