Flat urothelial carcinoma in situ (Clinging CIS) and small review por Jose R Paz

Patient: 67 years old female with hematuria.
Specimen: Trans urethral biopsy
Diagnosis: Flat urothelial carcinoma in situ (Denuded, Clinging CIS)

Flat urothelial carcinoma in situ (CIS) is a precursor of invasive transitional cell carcinoma (TCC). High-grade TCCs frequently are accompanied by CIS in surrounding urothelium. In contrast, superficial, noninvasive papillary TCCs are often low grade and generally are unaccompanied by CIS.

The proposed World Health Organization/International Society of Urological Pathology (WHO/ISUP) consensus classification of flat urothelial lesions expands the definition traditionally used for urothelial (transitional cell) carcinoma in situ (CIS), basing its diagnosis predominantly on the severity of cytologic changes.
Five major patterns of CIS are described, important to each pattern is the presence of high-grade cytologic atypia (*the defining feature*).

**The CIS patterns include:**

1. **Large cell CIS with pleomorphism**, the cells have abundant cytoplasm and nuclear pleomorphism.
2. **Large cell CIS without nuclear pleomorphism**.
3. **Small cell CIS**, the cells cytoplasm is relatively scant and pleomorphism is usually minimal.
4. **Clinging CIS**, the urothelium is denuded with a patchy, usually single layer of atypical cells.
5. **Cancerization of urothelium**, showing either pagetoid spread (in clusters or with isolated single cells) or undermining or overriding of the normal urothelium.

**Genetic and molecular markers** of urothelial premalignancy and malignancy have been subjected to intense studies. A primary target leading to low-grade papillary superficial bladder tumors resides on **chromosome 9**, while **p53** gene alterations are commonly seen in flat carcinoma in situ. Many non-invasive neoplasms have neither chromosome 9 nor p53 alterations. Studies have shown that many of the genes that are altered act upon the two recognized critical growth and senescence pathways, **TP53** and **RB** (retinoblastoma). Nevertheless, molecular alterations involving chromosome **9q** and the **INK4A** locus in **papillary superficial** tumors vs changes in chromosomes **14q and 8q**, **p53** and **RB** in **flat carcinoma in situ** lesions may indicate a molecular basis for early events that lead to varying pathways in urothelial tumorigenesis.

Fluorescent in situ hybridization (**FISH**) analysis of voided urine for amplification of **chromosomes 3, 7, and 17** and **deletion of 9p** has high sensitivity and specificity for diagnosing CIS in surveillance cases. Several other molecular markers, such as **NMP 22** and **BTA**, are under evaluation or used variably in clinical pathology.

**Immunohistochemistry** is used in the separation of urothelial carcinoma in situ (CIS) from reactive atypia. Using morphology alone may be difficult in some cases. An immunohistochemical panel is used to help in this differential diagnosis using antibodies against **CK20, p53, and CD44**.

**Normal urothelium,**
- **CK20** shows patchy cytoplasmic immunoreactivity in only the superficial umbrella cell layer.
- **CD44** stains only the basal cells.
- **p53** nuclear immunoreactivity varies from negative to weak and patchy.

**Reactive urothelium,**
- **CK20** immunoreactivity in only the umbrella cell layer.
- **CD44** overexpressed membranous stain in the *entire reactive urothelium*.
- **p53** nuclear staining is predominantly negative with occasional weak positivity in the basal and parabasal cells.

**Urothelium involved by CIS,**
- **CK20** intense positive stain all layers.
- **CD44** residual membranous stain of basal cells.
- **p53** positive nuclear stain all layers.
At least one positive immunomarker (CK20 or p53) should be expressed in cases of CIS. From a differential diagnosis perspective, use of a panel of all three antibodies with morphologic correlation is essential.

Illustration 2: p53 nuclear stain

Illustration 3: CK20 stain

Illustration 4: CD44 residual membranous stain of basal cells.