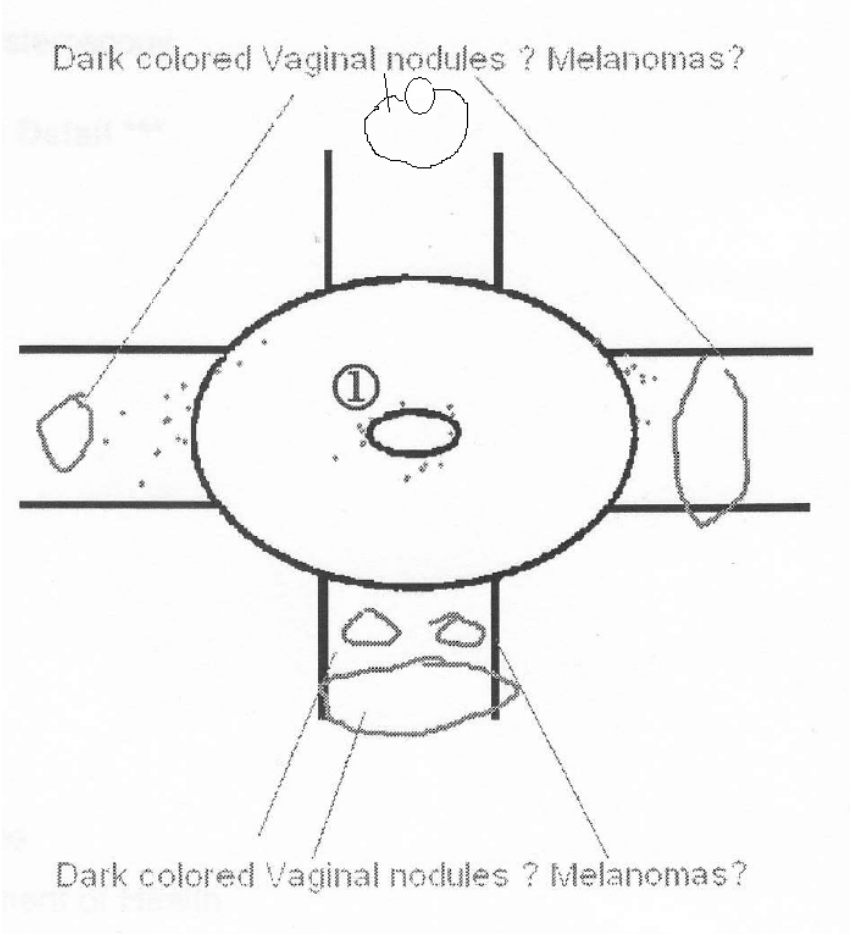
Case 1

- Madam TKC, 64 years old
- G3P2+1
- Menopaused with of PMB
- Good past health
- Cervical smear in private - AGC

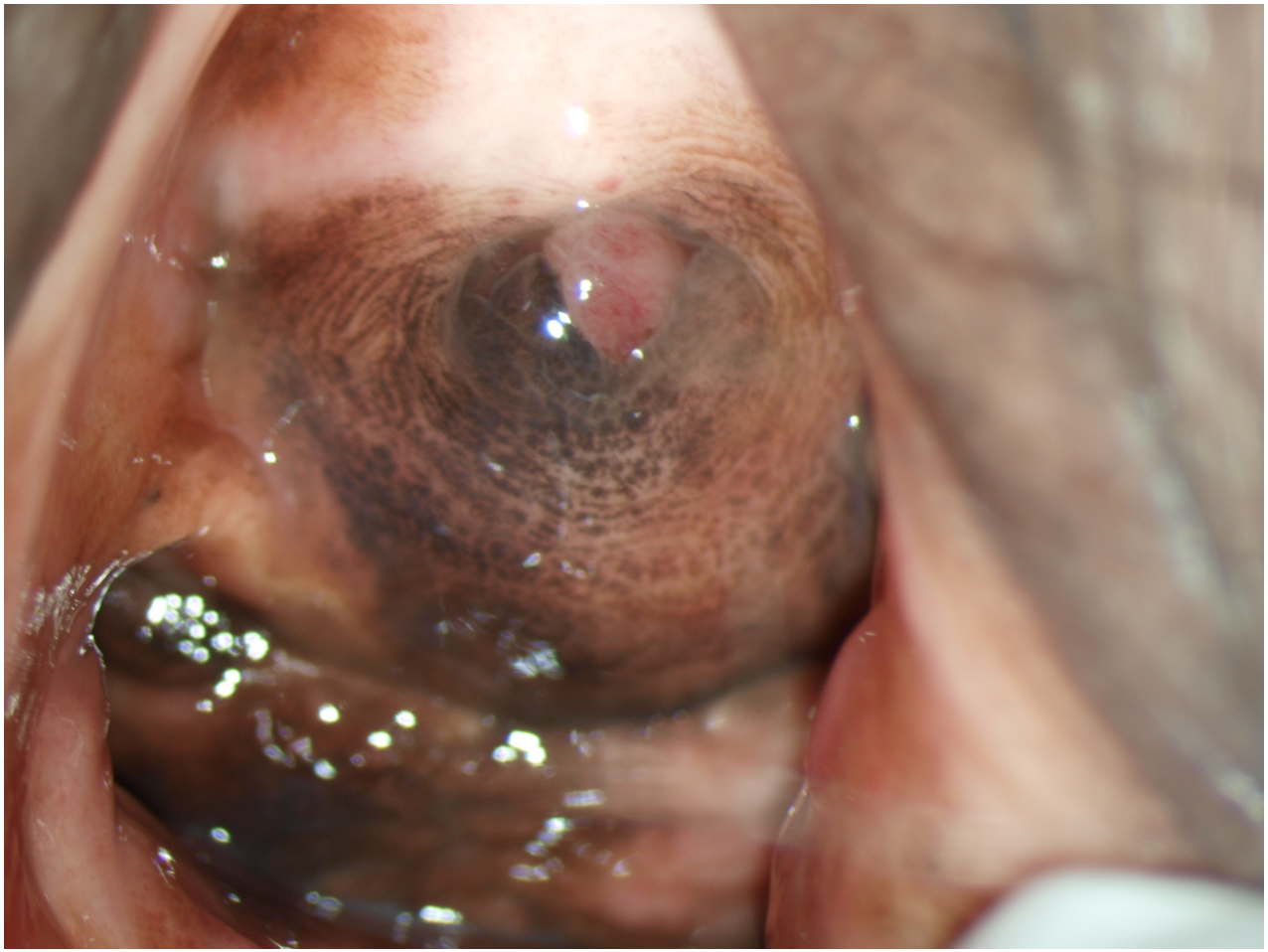
colposcopy



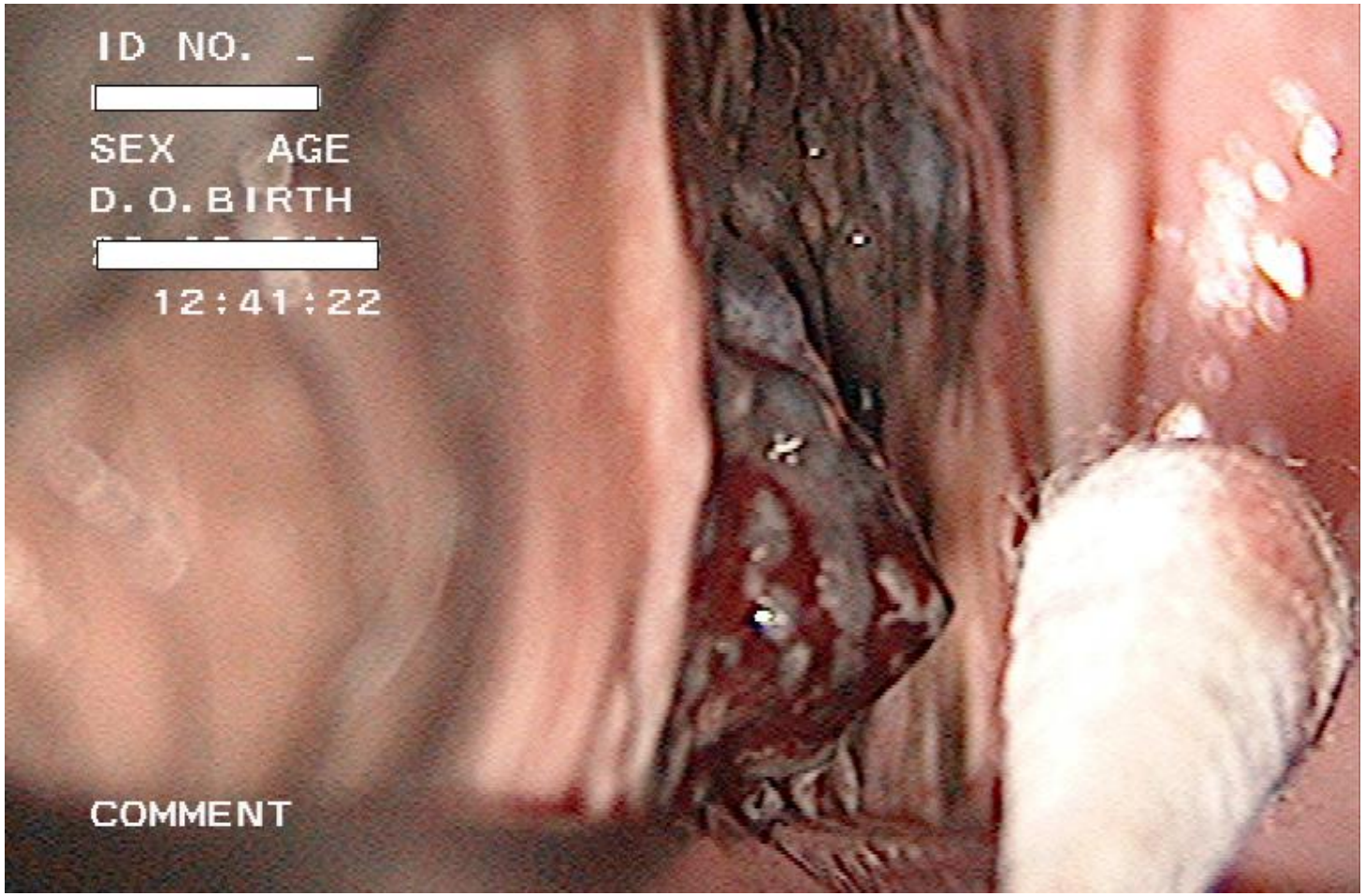
- Cervix
  - No gross lesion
  - suggestive of HPV
- Vagina
  - Dark coloured nodular lesions with contact bleeding
    - 12 OC around urethra, 2.5cm
    - 9 OC at introitus, 1cm
    - 6 OC at introitus, 2cm
    - 3 OC at mid-vagina, 2cm

» 4/2013

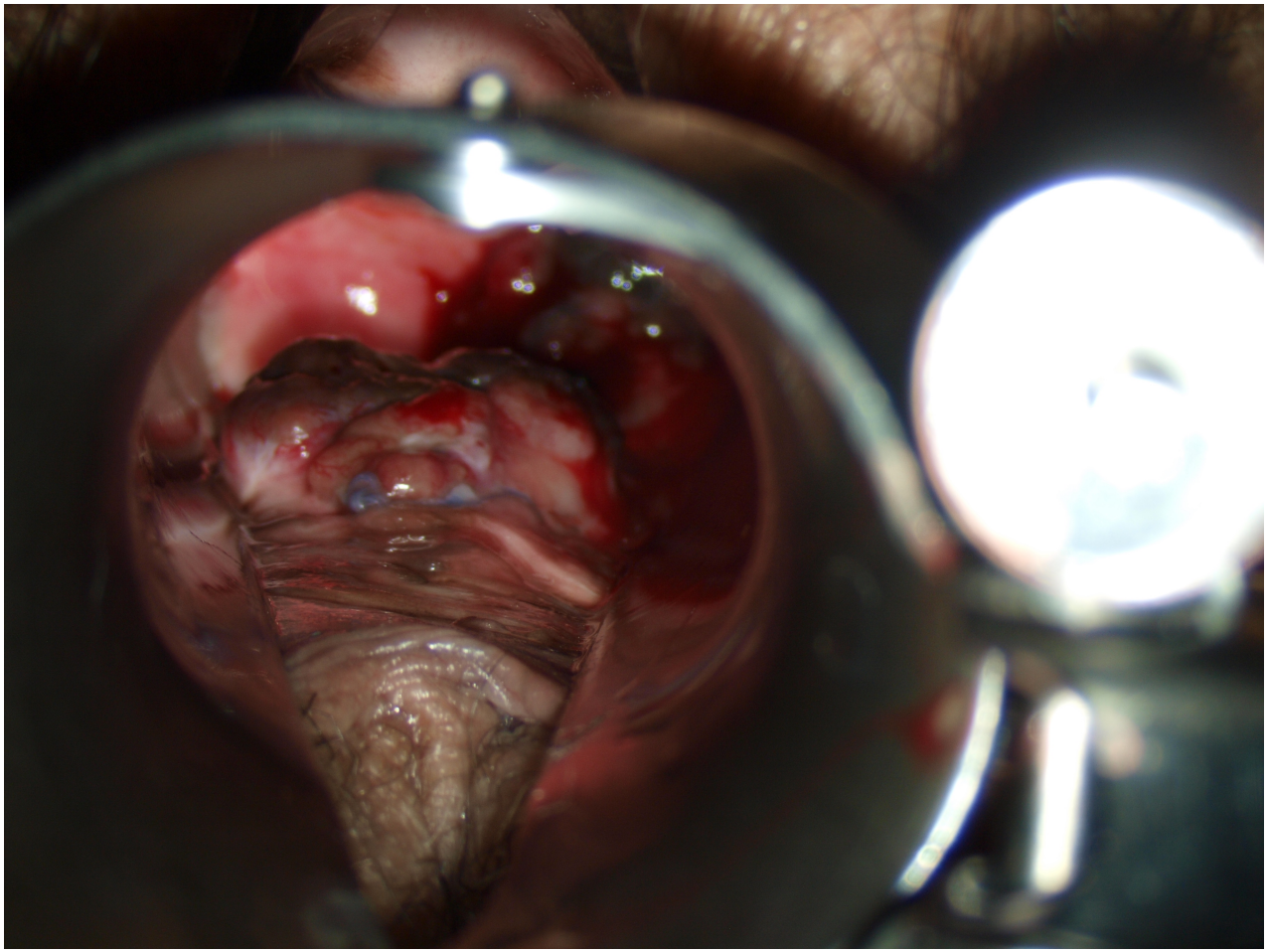
Colposcopy – vagina 12 OC around urethra



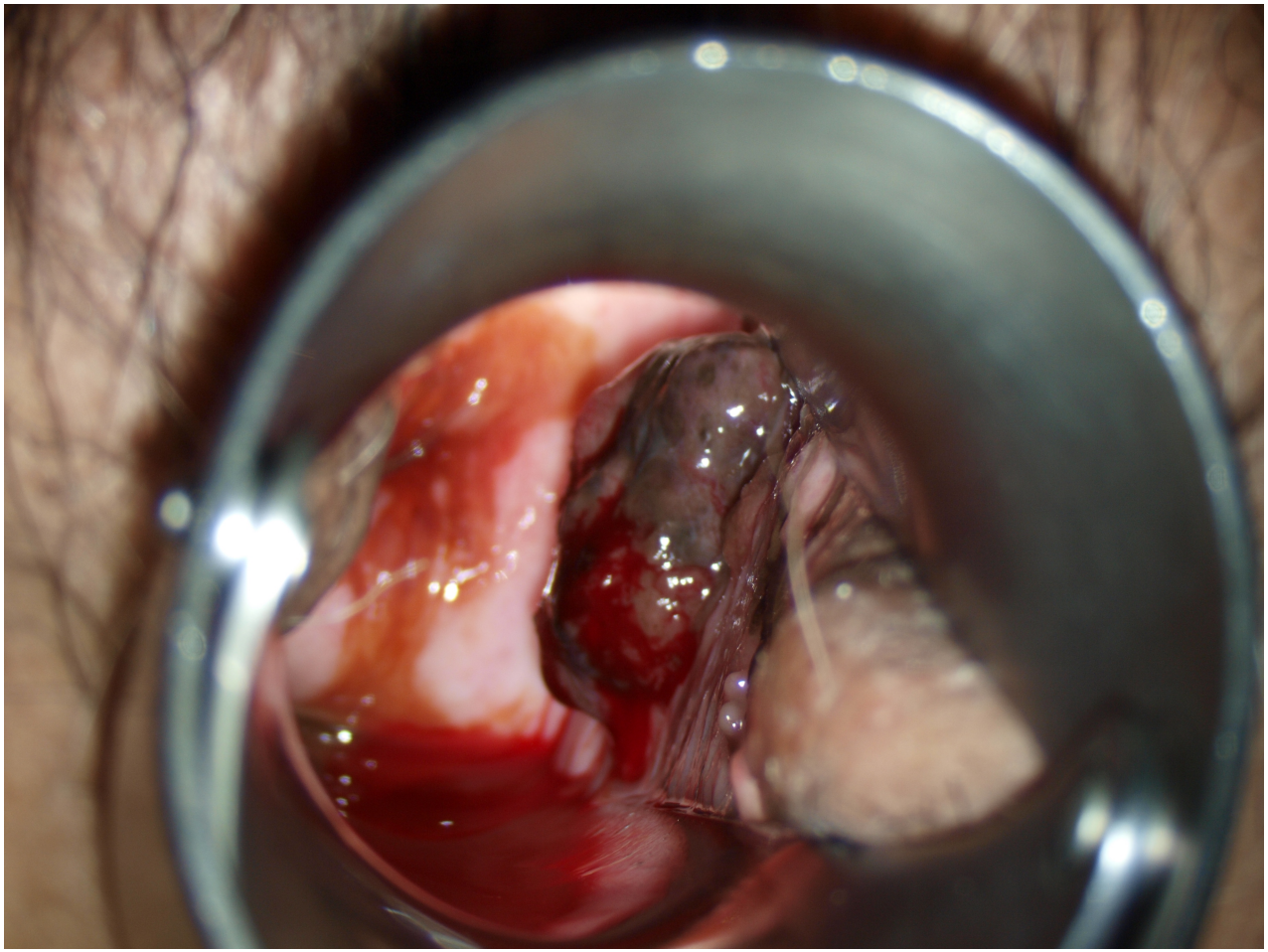
Colposcopy – vagina 9 OC introitus



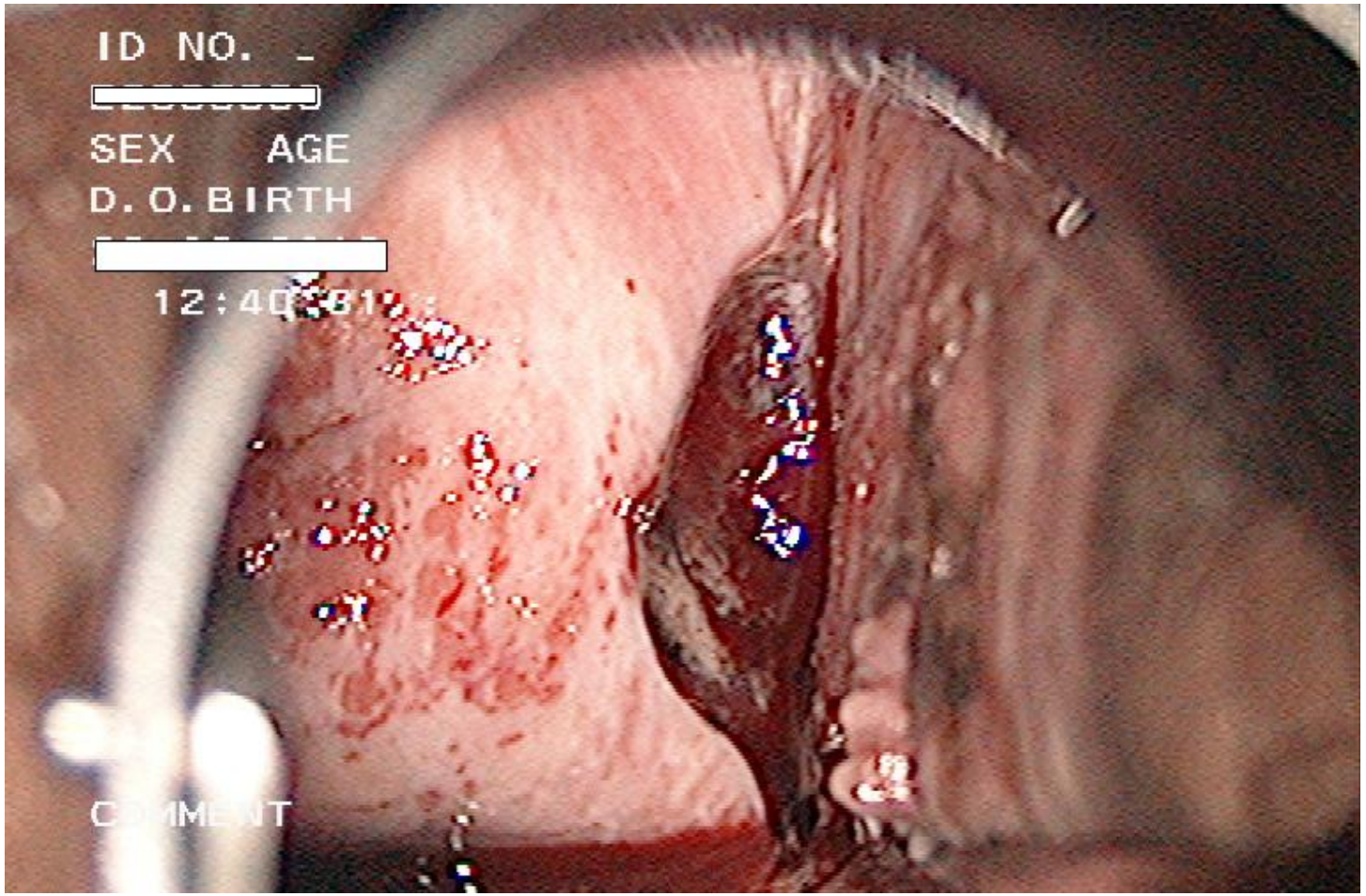
Colposcopy – vagina 6 OC introitus



Colposcopy – vagina 3 OC mid-vagina



Colposcopy - cervix



Pathological reports

- Cerivcal smear + cytobrush – ASCUS
- Vaginal biopsy 6OC
  - Macro-exam: grey red tissue 5mm, 7mm
  - Micro-exam: loose nests and trabeculae of pleomorphic cells with hyperchromatic nuclei, coarse chromatin and focal prominent nucleoli. There is moderate amount of eosinophilic cytoplasm, with some cells contain brown cytoplasmic pigments. No normal tissue is seen, Immunostain showed cells are MelA+ and AE1/3-.
  - Dx – **malignant melanoma**
- Cervial biopsy 11OC
  - A piece of squamous mucosa with intra-epithelial nests of epithelioid malignant cells showing nuclear enlargement and hyperchromasia, also demonstrate lentiginous growth and isolated pagetoid spread. Some are melanin-laden. Immunohistochemical staining : HMB45+, melanA+, variably S100+ and CK -.
  - Squamous cells are P16-, do not demonstrate a hig proliferative (Ki67) index, not pointing to a HGSIL
  - Isolated oval-spindly malignant cells in the stroma featuring stroma invasion, HMB45-, melanA- , S100+.
  - Dx – **malignant melanoma**
- ECC
  - Mlignant cell clusters with eosinophilic cytoplasm, marked nuclear pleomorphism and hperchromasia. Cytoplasmic melanin is discerned. HMB45+, melanA+, S100+, CK-
  - Dx – **malignant melanoma**

P/E and other investigations

- P/E
  - No pallor, no cervical LN
  - Abdomen: soft , no mass, no groin LN
  - PV :
    - Vulva : NAD
    - Vagina : as shown
    - Cervix: no gross lesion
    - Uteurs : normal sized, mobile
    - Fornices : clear
  - PR: free parametrium
- USG
  - Uterus - small, midline 2mm
  - Ovaries – not seen, no obvious adnexal mass
  - No free fluid
  - Kidneys – no hydronephrosis
  - Liver – no gross lesion

Imaging

- CXR – NAD
- PET-CT scan
  - Head and neck, thorax – NAD, no increase in FDG uptake suggestive of lung or liver involvement
  - Abdomen and pelvis
    - 2.4cm hypermetabolic lesion in vagina close to posterior urethra, SUVmax 3.4, compatible with history of vagianl melanoma
    - Hypermetabolic LN in bilateral external iliac regions, 1.5cm, SUVmax 2.2 and 1.8, suspicious of early nodal metastasis

Cervical melanoma

- Rare, 60 cases reported till 2008
- An exophytic, polypoid cervical mass that varies in colour (red, brown, grey, black or blue)
- Criteria
  - Melanin presence in normal cervical epithelium
  - Absence of melanoma elsewhere in the body
  - Presence of junctional activity in the cervical epithelium next to the lesion
  - Metastatic spread accords to pattern of cervical Ca
- Management
  - Early stage : RH + vaginectomy
  - Advanced stage : pelvic irradiation

Vaginal melanoma

- Rare
  - USA (cancer statistics 2009, National cancer data base 1998)
    - Primary Ca vagina 3% of female genital tract Ca
    - Malignant melanoma 5% of CA vagina
    - Overall incidence 0.46 cases / 1 million women per year

Vaginal melanoma

- Mean age 55 years old
- Symptoms: bleeding, a mass, discharge, dyspareunia, pruritus, pain, dysuria
- More common in lower 1/3 and anterior vaignal wall
- 25% amelanotic

Vaginal melanoma

- Poor prognosis
  - 5 year survival
    - Sweden 18% (Cancer 1993;71:1893-7)
    - USA 11.4% (all female genital tract melanoma, National cancer data base, Cancer 1998;83:1664-78)
    - MD Anderson cancer centre 20% (Obs Gyn, Vol 116, No. 6 Dec, 2010)
  - Median survival
    - 19 - 20 months (Ann Surg Oncol, vol.11 No.1,2003; Obs Gyn, Vol 116, No. 6 Dec, 2010)
  - Median recurrence free survival
    - 11.4 – 12 months
  - Recurrence
    - 82 - 89% (67% distant, 33% local)
  - Delayed diagnosis, rich vascular and lymphatic network
- Prognostic factors
  - Tumor size (<3cm Vs $\geqq$3cm)
  - Depth of invasion

Vaginal melanoma management

TABLE 4. *Review of previous reports from the literature*

Author	Year published	Years of accrual	No. of cases	5-y survival (%)	Conclusions
Bonner[7]	1988	24	10 (SI)	20	XRT followed by surgery preferred
Reid[8]	1989	52	15 (SI)	17	Type of surgery did not influence survival
Van Nostrand[9]	1994	21	8 (SI)	0	Improved survival with radical surgery
Konstadoulaskis[10]	1994	19	13 (SI)	54	Type of surgery did not influence survival
Irvin[4]	1998	20	7 (SI)	0	LR control may be achieved with XRT
Petru[3]	1998	14	14 (MI)	21	XRT an alternative to surgery
Cobellis[6]	2000	24	15 (SI)	0	Wide excision of tumor required
Current series	2003	24	35 (SI)	11	Surgical removal of gross disease optimal

SI, single institution; XRT, radiotherapy; LR, locoregional; MI, multiple institutions.

- cases series
  - Absence of prospective data
  - Large time span
  - Incomplete description of treatment modalities
  - Tendency to combine vulvar and vaginal lesions

Vaginal melanoma - modality

- Surgery Vs non surgical
  - Median survival
    - (A) 25 months Vs 13 months (P=0.039) (Ann Surg Oncol, vol.11 No.1,2003)
      - Memorial Sloan-Kettering Cancer Centre, 1977 – 2001, 35 patients,
      - FIGO staging : I (46%), II (17%), III (14%), IV (23%)
      - Local excision (WLE, vaginectomy) 12 pts + radical excision (WRE + TAH, exenteration) 12 pts, RT (5+6) pts
    - (B) 24.3 - 34.4 months Vs 8.7 months (P=0.01) (Obs Gyn, Vol 116, No. 6 Dec, 2010)
      - MD Anderson Cancer Centre, 1980 – 2009, 37 patients
      - FIGO stage I diseases,
      - Wide excision (WLE, WRE) 28 pts, exenteration 4 pts, RT/ Chemo/RT+chemo 5 pts
- Surgery remained the first line treatment

Vaginal melanoma - surgery

- Surgery
  - Conservative Vs Radical
    - Conservative – wide local excision, wide radical excision
    - Radical – vaginectomy +/- vulvectomy to pelvic exenteration
    - Median survival
      - (A) 10 months Vs 12 months (reucrrence free survival)
      - (B) 24.3 months Vs 34.4 months (overall survival)
      - (C) 1.9 years Vs 2.7 years (overall survival), 0.62 years Vs 0.49 years (recurrence free survival)
        - » Mayo clinic, 1993 – 2012, 14 patients, (Gyn Oncol 129(2013) 533-537)
      - Not statistically significant
    - No significant difference in survival

Vaginal melanoma - surgery

- Margins (adopted from cutaneous melanoma)
  - 1cm for $\leqq$ 2mm thick, 2cm for > 2mm thick
  - Resection margins
    - (A) 92% (22) complete resection, 71% (17) margin +ve, 82% (18) recurrence
    - (B) 83% (27) margin –ve, 89% (33) recurrence
    - (B) median survival: +ve 10.1 months, -ve 26.7 months (P=0.6)
    - Clear margin do not decrease recurrence survival, no difference in survival

Vaginal melanoma – LN dissection

- Regional lymph nodes
  - 8% - 25%
  - Prognostic significance (B)
    - median survival
    - +ve 10.1months Vs –ve 30 months (P<0.001)
  - ? Which nodal basins to resect
    - Lower 1/3 – groin
    - Apex - pelvis
  - ? Therapeutic benefits
  - ? Role of sentinal node

Vaginal malenoma - Radiotherapy

- Role of radiotherapy
  - Primary treatment: unable / unwilling for surgery
  - Pre-operative neoadjuvant to reduce tumor size and hence for a more conservative surgery
  - Post operative adjuvant
    - (B) WE + RT Vs WE alone (median survival)
      - 29.4 months Vs 16.1 months (P=0.46)
    - (B) Exeneration Vs WE + RT (median survival)
      - 34.4 months Vs 29.4 months
    - ? adjuvant RT after WE for better loco-regional control
  - Palliation of local symptoms due to metastasis

Vaginal melanoma
Chemo- / bio- therapy

- Chemotherapy, biotherapy
  - Traditional cytotoxic agents
    - Dacarbazine, temozolomide, platinum compounds
    - Limited or no success
  - Interleukin-2
    - No improvement in overall survival
    - Increased toxicity
  - Ineterferon-**α**
    - Extending recurrence free survival by 30%
    - No statistical benefit in overall survival
  - Neoadjuvant (C)
    - 1 patient, 3 cycles of Carboplatin + Paclitaxel, tumor reduction of 50% to 1x1cm,
    - Local excision + left PLND + right GND + 6 cycles of Carbo+ taxel with bevacizumab added to 5 cycles
    - Disease free for 5 yrs
  - FDA approved
    - Dacarbazine, Interleukin-2 for advanced melanoma
    - Interferon- **α** for adjuvant therapy of surgically resected high-risk disease

Management

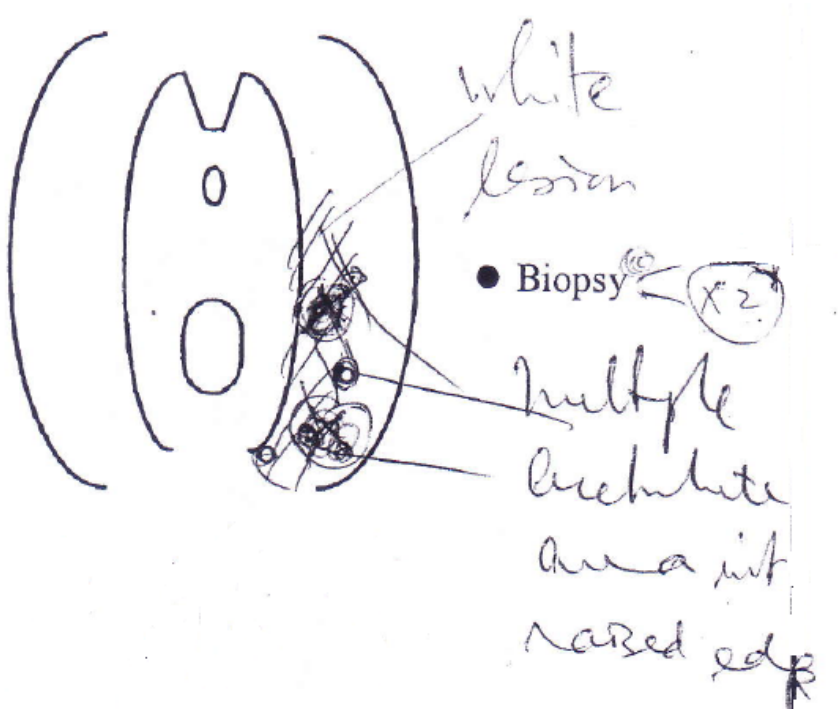
- Poor prognosis
- Surgery remained the first line treatment
- No significant difference in survival between radical and conservative surgery
- ? adjuvant RT after WE for better loco-regional control

- Madam TKC (O&G, Clinical oncology, urology)
  - Anterior exenteration + Mitrofanoff stoma +/- ileal conduit
  - +/- irradiation afterwards

Case 2

- Madam CSM, 64 years old
- G2P2
- TAH for fibroid in 1987
- Past health: hyperthyroidism in remission
- C/O pruritus vulvae for 7 years, not relieved by topical treatment from GPs
- Examination showed excoriation and leukoplakia over left labia majora

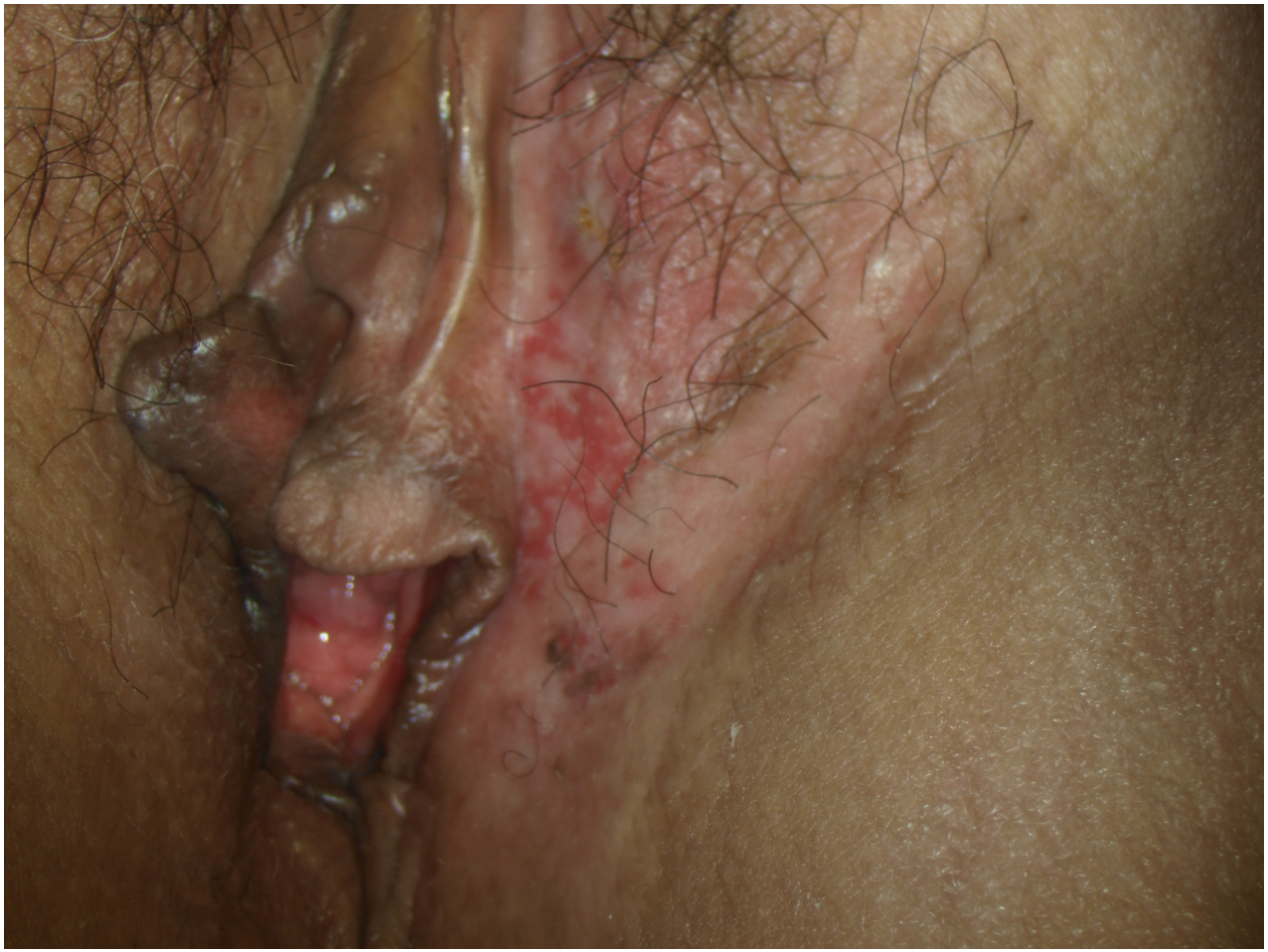
Colposcopy

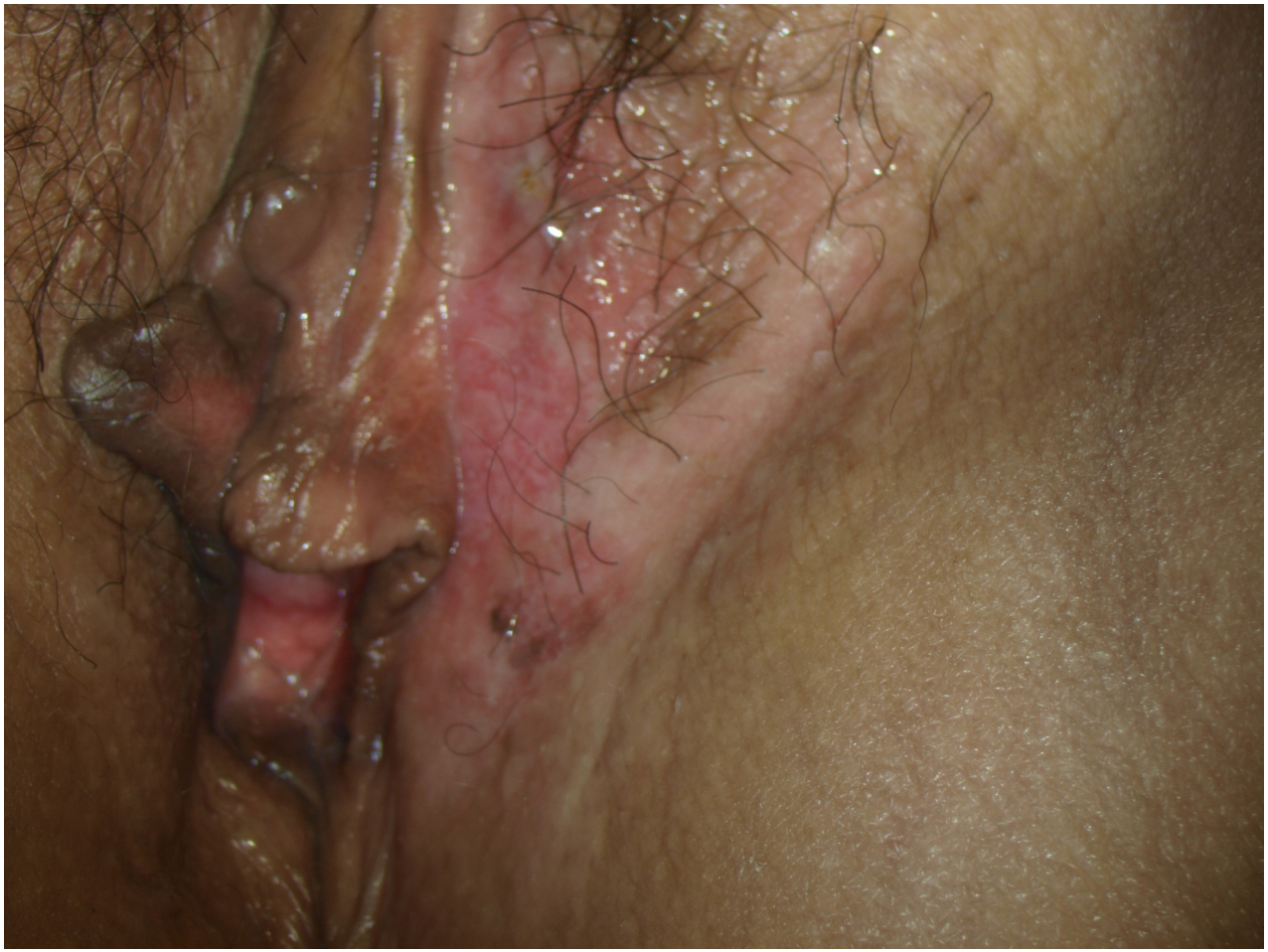


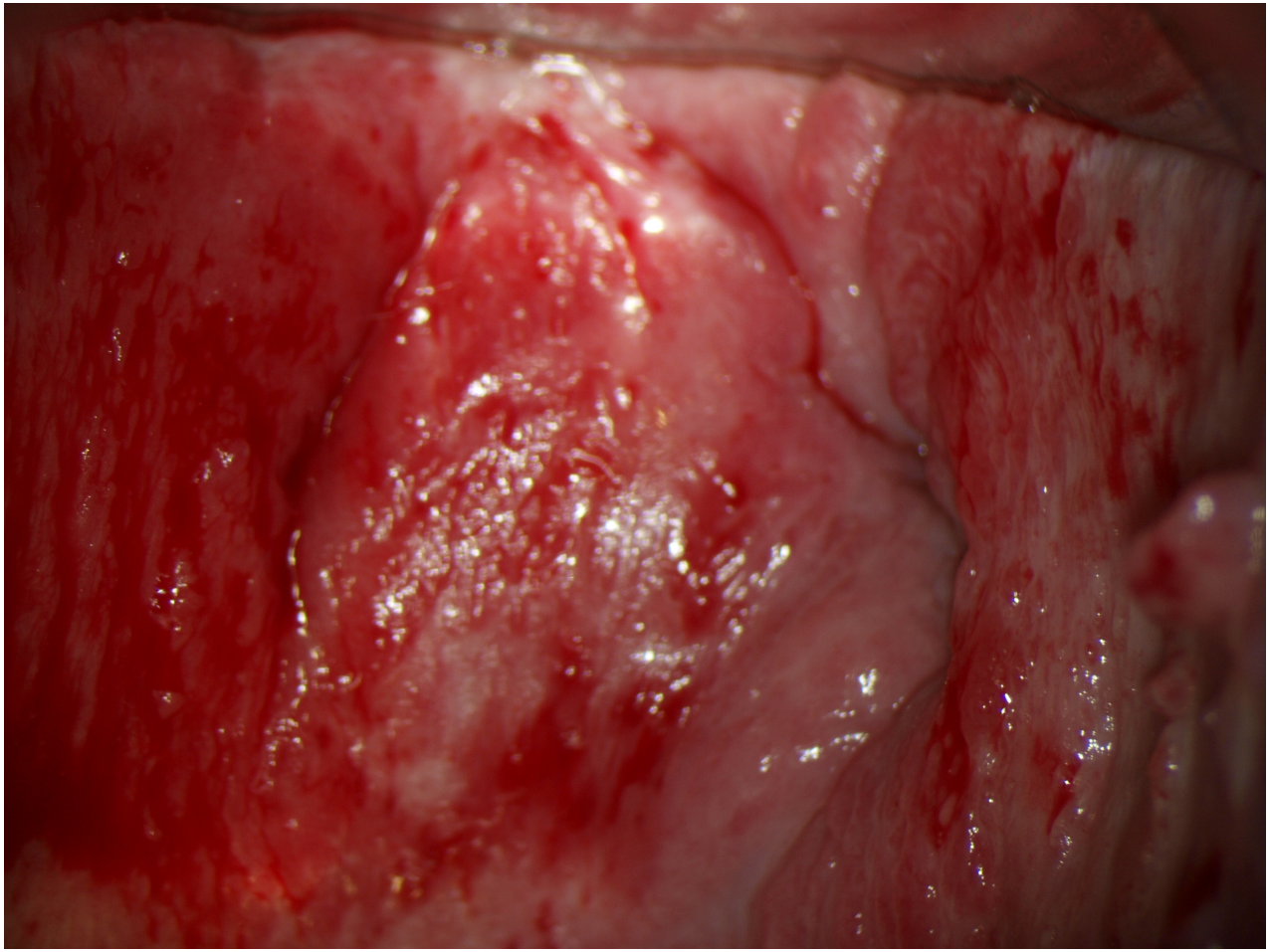
- Vulva
  - White lesion
  - Multiple aceto-white area with raised edges
- Vagina : NAD
- Dx :
  - ? Lichen Sclerosis
  - ? VIN lesion

» 17/6/2009

Colposcopy







Pathological reports

- Vulval biopsy
  - Vulvar squamous epithelium with large clear tumor cells forming solid nests and glandular space in epidermis. Clefts are noted between the rows of tumor cells. Scatter mcuin producitoh is seen. Immunohistochemistry for CAM5.2, CerbB2, BRST2 are positive, CK20 is negative
  - Dx: Extramammary Paget’ s disease

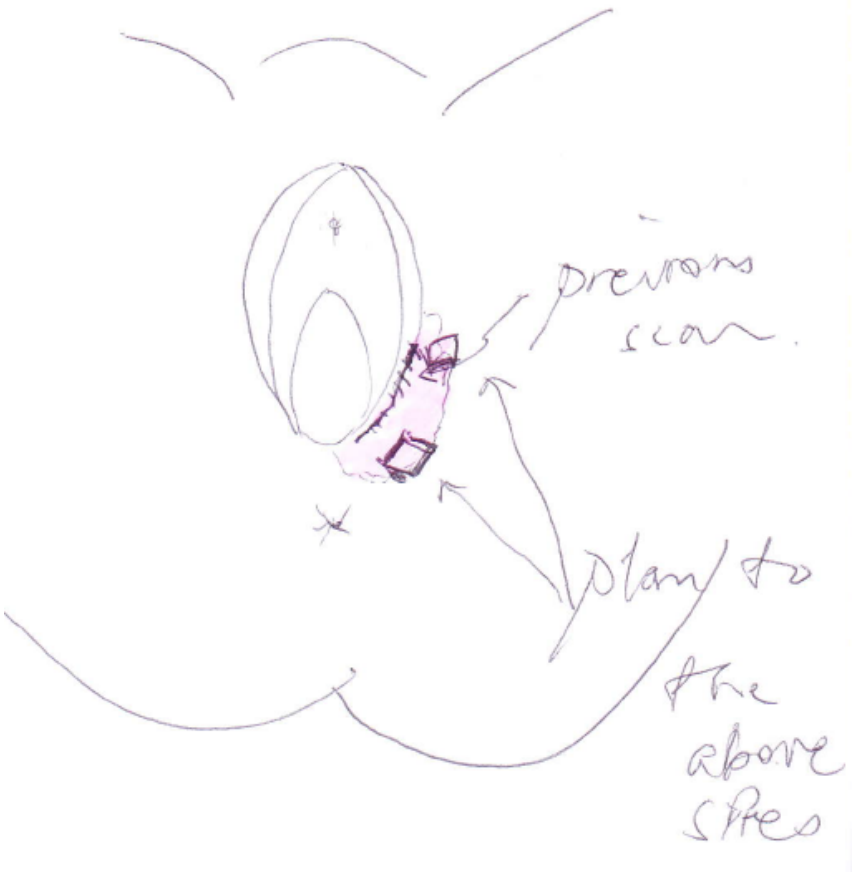
Management

- PE
  - No cervical, groin LN
  - Thyroid, breasts – NAD
  - Abdomens – soft, no mass
  - PV
    - Vulva and vagina – as shown
    - No pelvic mass
  - PR – no mass, no blood
- Surgical consultation
  - PET-CT done – no obvious FDG-avid lesion detected

Management

- 7/2009
  - Left hemi-vulvectomy
  - Pathology
    - Macro: 6.5cm x 3cm x 0.8mm
    - Micro: Extramammary Paget’ s disease, no invasive carcinoma, peripheral margins involved, deep margin is clear
- Follow up in 3 to 4 months
- 4/2011
  - Left vulva : slightly erythematous lesion at 5OC medial to previous scar
  - Biopsy : consistent with inflammed bartholin’ s duct

Management



- 10/2011
  - Slightly erythematous left vulva
  - Biopsy: 3, 5 OC – Extramammary Paget's disease
- 12/2011
  - Left wide local excision
  - Pathology
    - Macro: 7cm x 2cm x 0.5-1.0cm
    - Micro: Extramammary Paget's disease, no invasive carcinoma, 12OC margin, medial margin from 6-9OC involved
- 1/2013
  - P/E: no obvious lesion

Vulvar EMPD

- EMPD - 6.5% of all cutaneous Paget’ s disease
- EMPD - 65% in vulva, 20% perianal, 14% male genitalia
- Vulvar EMPD
  - 1-2 % of vulvar cancer
  - 50 to 80 years old
  - Symptoms: pruritus, burning, tenderness
  - Hx of non-specific and multiple topical treatment
  - A median delay of 2 yrs in diagnosis
  - Lesion
    - Primary lesion: erythematous, scaly plaque, raised, vulvety, well delineated, crusting, weepy erosion, ulceration, cake-icing appearance
    - Often hypopigmented rather than hyperpigmented

Classification

Classification (Proposed by Wilkinson and Brown, Hum Pathol 2000;33:549-55)

- Primary EMPD of vulva
  - a. Intra-epithelial Paget’ s disease
  - b. Intra-epithelial Paget’ s disease with stromal invasion
  - c. As a manifestation of an underlying adenoCA of a skin appendage or subcutaneous vulvar gland
  - 1a-75%, 1b-16%, 1c-9% (Int J Gynaecol Cancer 2006;16:1212-1215)
- Secondary EMPD of vulva
  - a. secondary to an anorectoal adenoCA
  - b. secondary to an urothelial CA
  - c. as a manifestation of another non-cutaneous adenoCA (eg. endocervical, endometrial, ovarian)

Association with internal malignancy

- Exact incidence remained unclear
- 10 – 64%
- Difficulties in interpreting results
  - Disparate definitions of internal malignancy
  - Precise chronology of the diagnosis
  - Unknown revolution relative to EMPD
  - Lack of uniform investigations
  - Retrospective studies: incomplete data, bias
  - Lack of correlation between the prevalence of various malignancies associated with EMPD relative to that seen by age group independent of EMPD
- Breast, GU tract (ovary, cervix, uterine, vulva, bladder), GI tract (oesophagus, stomach, pancreas, HCC, colon), thyroid..

- Primary EMPD with synchronous neoplasia
  - 5.3 – 8% (Int J Gynaecol Cancer 2006;16:1212-1215, J obstet Gynae 2004;24:124-125)

Prognosis

- Prognosis
  - Intra-epithelial, micro-invasive ($\leqq$1mm)
    - No death in median follow up of 68 months, 6.89 years (J Am Coll Surg 2003;196:45-50; Gyn Oncol 2000;77:183-9)
    - Standard mortality rate not statistically different from general population
  - Micro-invasion (up to level of papillary dermis)
    - No death → 88% 5 year survival (Br J Dermatol 2008;158(2):313-8; Gyn Oncol 1995;56:266-70)
  - Metastatic or with associated internal malignancy
    - Overall mortality 26% (J A, Acad Dermatol 1982;13(6):1009-14)
  - Factors associated with greater risks of death
    - Elevated CEA
    - Nodules in primary lesion, bliateral LN metastais
- Recurrence 30 – 60%

Evaluations

- History, review of systems
- Complete cutaneous examination
- Evaluate LN, liver, spleen
- Breast examination, Mammogram
- Gyneacological examination (colposcopy, cervical smear, pelvic USG)
- *Urologic evaluation (cystoscopy +/- uroscan)
- *Colonoscopy +/- CT scan
- Serum CEA (if with invasive EMPD)
  - » Department of dermatology, ST-Luc hospital, Quebec (Dermatol Clin 28 (2010)807-826)

- * in case of primary EMPD, some proposed procedures only if urethra or anus is involved

Treatment

- Surgery
  - WLE 2 – 3 cm beyond clinical margins
  - Down to 0.5cm of subcutaneous lesion

- Margin
  - Intra-operative FS
    - High rate of false negative, approaches 40%
    - Limited use in multicentric disease
  - Margin status - little effect on disease outcome
  - Disease recurrence is common regardless of surgical margin status (Gyn oncol 104(2007)547-550)
    - Recurrence 70% (margin +ve) Vs 38% (margin -ve)
    - No correlation (P=0.20) between disease recurrence and margin status with a median follow up of 49 months (3-186 months)

Treatment

- LASER
  - Painful
  - Lack of histology
- Photodynamic therapy
- CO2 LASER + photodynamic therapy
- 5-FU
  - In combination with surgery
  - Monotherapy – clinical clearance but not pathological clearance
- Imiquimod cream
  - Both clinical and pathological clearance reported
  - Could be considered as alteranative or adjunct to surgery
- Interferon-A, necrosis factor-A
- Bleomycin
- Radiotherapy

Surveillance

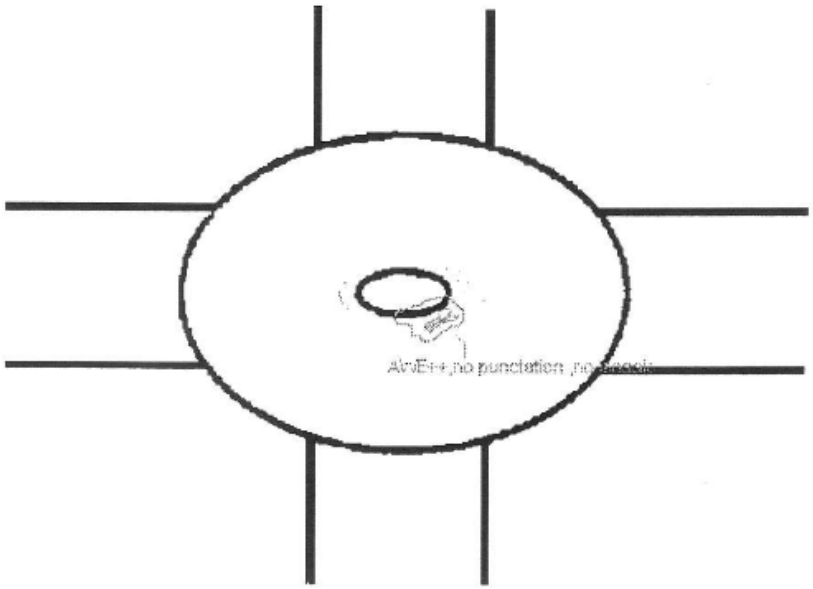
- Primary noninvasive EMPD
  - Clinical evaluation twice a year in first 3 years, then once yearly there after
  - Internal malignancy screening directed towards particular signs or symptoms thereafter
- Secondary EMPD
  - Clinical evaluation 3 – 4 times per year
  - Repeated yearly screening directed to site of lesion

» Department of dermatology, ST-Luc hospital, Quebec (Dermatol Clin 28 (2010)807-826)

Case 3

- Madam CQH, 41 years old
- G2P1+1
- Past health : good
- asymptomatic
- Smear : ASCUS, HR HPV +ve

Colposcopy



- AW ++
- No punctation
- No mosacism
- Dx : HPV, CIN 1, 2
- Biopsy at 5, 6 OC

Pathological reports

- Biopsy at 5 OC
  - CIN 1, HPV
  - Dx: Lymphoid infiltrate consistent with lymphoma-like lesion
  - Microscopic description
    - Transformation zone cervical tissue with koilocytosis and CIN 1
    - A superficial band of lymphoid cells with increased number of large cells which show mildly irregular nuclear contour. The large cells are mainly at the more supercicila level, while small cells are also present. Whte the large cells are maily CD20+ B cells with high proliferative inde and the small cells are maily CD3+ T cells, the infiltrate is still most consistent with a lymphoma-like lesion due to its superficial non-expansile nature. This probably represents an eaggerated inflammatoryu reaction in the cervix
- Biopsy at 6 OC
  - CIN 1, HPV