Reviewer’s report

Title: Implication of Human Papilloma Virus-66 in vulvar carcinoma: a case report

Version: 1 Date: 18 July 2010

Reviewer: Reinhard R Kirnbauer

Which of the following best describes what type of case report this is?: Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: Yes

Does the case report have diagnostic value?: Yes

Will the case report make a difference to clinical practice?: Yes

Is the anonymity of the patient protected?: Yes

Comments to authors:

Comments for the Authors

The authors report on an interesting case implicating high-risk HPV 66 as causative agent in the pathogenesis of metastasizing vulvar carcinoma in an elderly women without previous pathological gynecological history. The presence of HPV 66 was demonstrated by molecular biological methods, the absence of other most common mucosal high-risk HPV types and low-risk HPV types was attributed to negative results by Hybrid Capture 2 test.

Abstract:

Introduction part:
1st line: „Vulvar carcinoma in elderly women is hardly associated with infection of any type of HPV“
The term „hardly may be replaced by „less often“.

3rd line: „There is no reported case demonstrating and verifying direct and exclusive correlation between HPV-66 typing and vulvar cancer“.
There is a paper reporting on a HPV 66 and HPV 52 positive vulvar carcinoma. Cancer Epidemiol Biomarkers Prev. 2009 Jul;18(7):2061-7. The etiologic role of HPV in vulvar squamous cell carcinoma fine tuned. van de Nieuwenhof HP, et al. The authors may want to cite this reference and change the above mentiones sentence and adapt the introduction.

Case presentation part:
3rd line: „HPV66 genotype was detected through cytological examination and HPV DNA typing“.
Detection of HPV 66 cannot be performed by cytological examination. Please correct.

Conclusion part:
3rd line. „Suspicious lesions should be treated likewise“.
The authors may want to specify this statement.

Introduction:
1st line: „Vulvar carcinoma in elderly women is only rarely associated with any type of HPV infection.“.... The terms „only rarely“ shall be omitted and be replaced by more precise data and a reference.
The authors may want to define type 1 and 2 vulvar carcinoma.

Case presentation:
1st line: „with a free obstetric and gynaecologic history”
The authors need to specify this.
7th line: „labia majus“.
The singular is LABIUM MAJUS. Please correct. See also Figure legend 1

3rd paragraph: „histopathological examination revealed the presence of SCC arising from a vulvar condyloma“.
The authors may comment on invasion of the SCC.
The terms „arising from a vulvar condyloma“ shall be deleted and changed to VIN. Especially as Figure 3 shows “The adjacent squamous epithelium exhibited VIN-I and VIN-II”. The authors may want to correct this contradiction.

4th para, 6th line:
Please specify „focal to extended metastases“. 
5th para

„In the specimen obtained by liquid-based Cytology techniques...“

Where did the authors take the specimen for liquid-based cyto?

Can HPV 66 DNA also be detected e.g. by PCR and Clinical Arrays in the metastases of the regional lymph nodes?

Additional experiments should have been performed to establish HPV as the causal link between tumor, metastases, VIN and condyloma. E.g. In situ hybridization experiments aimed at the detection of E6 and E7 transcripts and of the viral DNA in sections of the tumor metastases, VIN and condyloma would have identified the cells expressing the viral genome and the cells productively infected (vegetative viral DNA replication).

Conclusion:

1st Para, 1st line: „The relation of HPV-infection to anogenital squamous neoplasia in women is well established and usually encountered in patients with genital condylomatosis“

The latter statement is wrong and shall be deleted.

2nd para, 1st line:

„HPV-66 genotype is reported to be mainly associated with cervical squamous carcinoma“


3rd para

„In conclusion, albeit rare, in patients with HPV-66 infection the possibility of a coexisting invasive malignancy, even in the presence of benign lesions, should be considered.“

My conclusion would rather be that Hybrid Capture II test does not detect all high-risk HPV types and that negativity does NOT rule out vulvar cancer, esp. in older women’s cancer, as the majority of these cancers are HPV negative. More sensitive tests like PCR with degenerate primers are required to establish HPV infections such as HPV 66 as causal.

Acknowledgements:

„We recognize with respect Dr. Kartsiounis Christos, head of the department of gynecologic oncology for his help:“

Please rewrite: „We recognize Dr. Kartsiounis Christos for his help“ and specify his contribution.

Figures:
The histological illustrations are good, however, Figure 1 seems to be a bit blurred. The authors may want to replace this picture.

Figure legends.
Figure 1. Labium majus.
Fig.2.+3. Histological figures are poorly described. The authors may add something about invasion, dysplasia, inflammatory infiltrate etc...
Figure 4. „Koilocytotic changes in vulvar squamous epithelium. These are diagnostic of HPV infection“
Replace “diagnostic” with “consistent with”
Figure 5. „Clinical Arrays Technique used for HPV typing. The combination of the three dark diagonal points indicated the presence of the HPV-66 typing“
The authors should explain all the other less prominent dots.

**Quality of written English:** Not suitable for publication unless extensively edited