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# Table of Contents

## Original Articles

- **Phase II/III Randomized Controlled Trial of Concomitant Hyperfractionated Radiotherapy plus Cetuximab (Anti-EGFR Antibody) or Chemotherapy in Locally Advanced Head and Neck Cancer** ................................. 06  
  Khaled Al–Saleh, Mustafa El–Sherify, Reham Safwat, Amany Elbasmy, Jitendra Shete, Amany Hussein, Marwa Nazeeh, Ahmad Bedair

- **Betel Chewing: A New Analysis, In Vitro and In Vivo, of the Risk Factors in Oral Cancer** .......................................................... 13  
  Roberto Menicagli, Ortensio Marotta, Maione Nunzia, Casotti Maria Teresa

- **Retrospective Analysis of Outcomes of Patients with Relapsed, Refractory and Metastatic Sarcomas who have received Metronomic Chemotherapy** ........................................................................................................ 22  
  Santhosh Kumar Devadas, Sripad Banavali

- **Does Adjuvant Chemotherapy for Locally Advanced Resectable Rectal Cancer treated with Neoadjuvant Chemoradiotherapy have an impact on survival? A Single Moroccan Institute Retrospective Study** ........................... 29  
  Youssef Seddik, Sami Aziz Brahmi, Said Afqir

- **A Multicenter Study of the Impact of Body Mass Index (BMI) on the incidence of Pathologic Complete Response (pCR) Among Saudi Patients with locally advanced Breast cancer (LABC) post Neoadjuvant Chemotherapy (NAC)** ........................................................................................................ 33  

- **Effects of Tualang Honey on Cancer Related Fatigue: A Multicenter Open–label Trial of H&N Cancer Patients** ................................. 43  
  Viji Ramasamy, Norhafiza binti Mat Lazim, Baharudin Abdullah, Avatar Singh

- **The Incidence and Clinical Significance of Atypical Glandular Cells of Undetermined Significance on Cervical Pap Smears** ............... 52  
  Ehab Al–Rayyan, Mitri Rashed, Maher Maaita, Sultan Qudah, Omar Taso, William Haddadin

- **Total or Subtotal Colectomy with Primary Anastomosis for Occlusive Left Colon Cancer: A Safe, Acceptable and Applicable Procedure** ........................................................................................................ 57  
  William A. Nehmeh, Michel Gabriel, Ahmad Tarhini, Ghassan Chakhtoura, Riad Sarkis, Bassam Abboud, Roger Noun, Cyril Tohmé

- **Descriptive Study of Nasopharyngeal Carcinoma and Treatment Outcomes: An Eight Years Experience in Hadhramout National Cancer Centre, Yemen** ................................................................. 61  
  Abdulrahman Ali Bahammam, Ahmed Mohammed Badheeb, Samir Yeslam Baothman

## Review Articles

- **Preoperative Denosumab plus Surgery in the Management of Giant Cell Tumor of Bone: A Comprehensive Narrative Literature Review** ........................................................................................................ 67  
  Ahmed Abu–Zaid, Sadiq Issa Alaqaili, Syed Osama Ahmad, Ibrahim Bin Hazzaa, Hani Alharbi

## Case Reports

- **Malignant Pleural Mesothelioma: A Multi–Disciplinary Approach** ........................................................................................................ 76  
  Muhammad Atif Mansha, Nasir Ali, Shaukat Ali, Nausheen Azam, Agha Muhammad Hammad Khan

- **Stage 4S Neuroblastoma: A Report of Two Cases Presenting with Extremes of Biological Behavior** .................................................. 81  
  Mohamed Mubarak, Arbinder Kumar Singal, Ashok Gawdi

## Conference Highlights/Scientific Contributions

- **News Notes** ........................................................................................................... 85

- **Advertisements** ..................................................................................................... 88

- **Scientific events in the GCC and the Arab World for 2019** ................................. 89
Original Article

The Incidence and Clinical Significance of Atypical Glandular Cells of Undetermined Significance on Cervical Pap Smears

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Abstract

Objective: To determine the incidence and the association between atypical glandular cells (AGC) reported on cervical pap smears and the underlying malignant and pre-malignant genital tract pathology.

Methods: A retrospective study was performed on the files of women who were had attended our colposcopy clinic at King Hussein Medical Centre (KHMC), between April 2014 and April 2018. Out of 8483 cervical pap smears reviewed, 68 patients have smears reported to be atypical glandular cells of undetermined significance (AGUS). Proper evaluation and follow up was available for 62 patients by performing colposcopic examination, repeating pap smear, proper biopsies and histological results. The factors considered included patients age, parity, symptoms, presence of pregnancy, smoking habits, hormonal therapy usage, colposcopic finding, and histological results of biopsies performed. Data were analyzed and comparison was performed between malignant and pre-malignant lesions.

Results: 68 cases of AGUS pap smears were identified out of 8483 cases reviewed forming incidence of about (0.8%). Of 62 patients with AGUS pap smears, twenty-two cases (32.3%) were found to have clinically significant malignant lesions on subsequent histological follow up. It included 12 cases of endometrial adenocarcinoma, 5 cases of adenocarcinoma of cervix, 3 cases of squamous cell carcinoma of cervix and 2 cases with secondary metastasis to vagina.

Of the 62 patients with AGUS pap smears, fourteen cases (20.6%) were found to have pre-malignant lesions. This included 7 cases of endometrial hyperplasia, 3 cases of adenocarcinoma in situ of cervix (ACIS) and 4 cases with cervical squamous intra-epithelial lesions.

Abnormal vaginal bleeding was the most common presenting symptom (30.6%); Woman above the age of 40 years and especially post-menopausal were more likely to have significant histological abnormalities.

Conclusion: Though the incidence of AGUS is low, it still important and clinically significant due to high substantial risk of having underlying premalignant or malignant lesions. Colposcopy and directed biopsy, endo–cervical curettage and endometrial biopsy should be performed to all women with AGUC especially to those above the age of 40 years, menopause, or having abnormal vaginal bleeding.

Keywords: Pap smear, atypical glandular cells, cervical neoplasia

Introduction

Cervical pap smears with atypical glandular cells of undetermined significance (AGUS) was introduced as a new histopathological diagnostic term in 1988, and since then it caused a huge dilemma in patient’s diagnosis and management. The criteria for diagnosis of AGUS pap smears is not clear, and it describes cells that can’t be considered reactive and neither neoplastic. The origin of atypical cells may be from cervix, uterus, vagina and any adjacent organ with glandular lining including those having underlining squamous pathology. Many studies reported the rate of discovering a significant clinical lesion among cases with AGUS pap smears ranging from 17% to about 80%. AGUS can be related to several benign conditions as...
well as malignant and premalignant lesions. This included inflammation, endometriosis, polyps, adenocarcinoma in situ, adenocarcinoma of cervix and uterus. (3,4,5)

Methods

This study was performed over a period of 4 years (from April 2014 to April 2018). A retrospective study was performed on the medical records of all women who attended our gynecology clinic at King Hussein Medical Centre (KHMC) after taking the approval of the hospital’s ethics committee to review those patients’ medical files.

Among 8483 pap smears reviewed, 68 patients had smears reported to be atypical glandular cells of undetermined significance (AGUS) with over all incidence of 0.8%. Proper evaluation and follow up data were available for only 62 patients.

The AGUS reports reviewed were not qualified neither by site nor by other criteria differentiating reactive changes from neoplastic cells.

The collected data from patients’ files consisted of patient’s age, parity, presenting symptoms, menopausal status, reason of referral to our clinic, presence of pregnancy, smoking habit and hormonal replacement therapy usage. In addition, the results of clinical and histological evaluation of AGUS pap smears were retrieved including colposcopic findings and histopathological results for all biopsies performed. The biopsies included ectocervical biopsy, endocervical curettage (ECC), loop electrosurgical excision of cervix (LEEP), cone biopsy of cervix, endometrial biopsy (EMB) and hysterectomy specimen performed when indicated.

All the AGUS pap smears included in our study were reviewed by a senior single cytopathologist. Two groups were created the first for cancer cases and the second group was for pre-cancer cases. Data were analyzed and compared between the two groups using the chi-square test with P-value <0.05 was considered statistically significant.

Results

Out of 8483 pap smears reviewed, 68 cases were identified with a report of AGUS pap smears during the four-year period of study, with a percentage of about 0.8%.

Patient’s age ranged from 28 –76 years, with mean age 48.2 years. Table 1 shows the main single cause for patient’s attendance to our gynaecology clinic. The most common reason was the presence of abnormal vaginal bleeding (19/62) forming about 30.6% of all cases. The abnormal bleeding was in the form of post-menopausal bleeding, post coital bleeding, intermenstrual bleeding, or prolonged heavy periods. This was followed by abnormal—looking cervix 12/62 (19.4%). 16.1% of patients presented with abnormal vaginal discharge in the form of recurrent vaginal infections (10/62). Nine out of 22 cases (14.5%) presented with abnormal pap smears. Eight cases (12.9%) attended clinic for routine pap smear check forming Only 6.5% of cases (4/62) had attended due to other causes like chronic pelvic pain, dysmenorrhea, dyspareunia, and other causes.

<table>
<thead>
<tr>
<th>Chief complaint</th>
<th>Number of cases (62)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine checking</td>
<td>8</td>
<td>12.9%</td>
</tr>
<tr>
<td>Abnormal pap smear</td>
<td>9</td>
<td>14.5%</td>
</tr>
<tr>
<td>Abnormal bleeding</td>
<td>19</td>
<td>30.6%</td>
</tr>
<tr>
<td>Abnormal discharge</td>
<td>10</td>
<td>16.1%</td>
</tr>
<tr>
<td>Abnormal looking cervix</td>
<td>12</td>
<td>19.4%</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

Table 1: The main single cause for patient’s attendance to clinic (62 cases)

Table 2 revealed the colposcopic finding during clinical evaluation for patients with AGUS pap smears. Malignant lesions were recognized in 12.9% of cases (8/62), while pre malignant lesions in the form of cervical dysplasia were identified in 11.3% of cases (7/62). Most cases with AGUS pap smears had a normal looking cervix or vagina during colposcopy evaluation, 34/62 cases forming 54.8% of all cases evaluated. Unsatisfactory colposcopic evaluation were reported in 9/62 cases forming 14.5%. Only 6.5% (4/63) cases had other colposcopic findings in the form of infection, atrophy and others.

<table>
<thead>
<tr>
<th>Colposcopic finding</th>
<th>N (62)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsatisfactory</td>
<td>9</td>
<td>14.5</td>
</tr>
<tr>
<td>Normal</td>
<td>34</td>
<td>54.8</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>7</td>
<td>11.3</td>
</tr>
<tr>
<td>Malignancy</td>
<td>8</td>
<td>12.9%</td>
</tr>
<tr>
<td>Others (infection, atrophy)</td>
<td>4</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Table 2: Colposcopic finding for clients with AGUS Pap smears (62 cases)

Table 3 summarizes the final histopathology results from different collected biopsies. Thirty-six cases out of sixty-eight (52.9%) had a final diagnosis with either cancerous or pre—cancerous conditions. Fourteen cases were diagnosed with pre—cancer conditions forming 20.6% of all cases. Four cases were squamous intraepithelial lesions, seven cases endometrial hyperplasia and three
Atypical Glandular Cells on Pap Smear Reports, Ehab Al-Rayyan, et. al.

with adenocarcinoma in situ forming 5.9%, 10.3% and 4.4% respectively. Twenty-two cases were diagnosed with cancer conditions forming 32.9%. Twelve cases had endometrial adenocarcinoma (17.6%), five cases cervical adenocarcinoma (7.4%), three cases had squamous cell carcinoma of cervix (4.4%) and two cases were secondary metastasis to vagina (2.9%) one from ovarian cancer and the other from colonic cancer.

<table>
<thead>
<tr>
<th>Histopathological diagnosis</th>
<th>N (68)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous Intraepithelial Lesion (SIL)</td>
<td>4</td>
<td>5.9%</td>
</tr>
<tr>
<td>Endometrial Hyperplasia (EH)</td>
<td>7</td>
<td>10.3%</td>
</tr>
<tr>
<td>Adenocarcinoma in Situ (ACIS)</td>
<td>3</td>
<td>4.4%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>14</td>
<td><strong>20.6%</strong></td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma of uterus</td>
<td>12</td>
<td>17.6%</td>
</tr>
<tr>
<td>Adenocarcinoma of cervix</td>
<td>5</td>
<td>7.4%</td>
</tr>
<tr>
<td>Squamous cell carcinoma of cervix</td>
<td>3</td>
<td>4.4%</td>
</tr>
<tr>
<td>Secondary metastasis to vagina</td>
<td>2</td>
<td>2.9%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>22</td>
<td><strong>32.3%</strong></td>
</tr>
</tbody>
</table>

Table 3: Histopathology summary of biopsy results discovered in (62) cases with AGUS pap smears

Table 4 shows the comparison between patients who have pre-cancerous and cancerous conditions. Patients older than 40 years, 20/22 cases (90.9%), were diagnosed as cancer patients compared to 9/14 cases (64.3%) who were diagnosed with precancerous conditions. Patients with low parity (had two babies or less) 10/22 cases (45.5%) had cancer conditions while patients with pre-cancer conditions were 4/14 (28.6%) and the remaining of the two groups were for patients who had three and more babies. Most patients who were diagnosed with cancer were postmenopausal 18/22 (81.9%) as compared to 50% for patients with pre-cancer conditions 7/14. Only one patient had AGUS pap smear while she was pregnant and was diagnosed with a pre-cancer lesion as cervical dysplasia. The most common symptom revealed is having abnormal vaginal bleeding. It was identified in twenty-one cases out of 22 (95.4%) in patients with cancer lesion and 12/14 cases (85.7%) in pre-cancer cases. 50% of patients who were diagnosed with cancer condition were current smokers compared to 57.1% for patients who were diagnosed with pre-cancer conditions. Hormone replacement therapy was used in 4/22 cases (18.2%) with cancer and 2/14 (14.2%) with pre-cancer conditions. However, all the formal data had a p-value > 0.05 and therefore were statistically nonsignificant which may be due to small number of patients at each group.

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Cancer (n: 22) percentage</th>
<th>Precancer (n: 14) percentage</th>
<th>P–Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of abnormal Vaginal bleeding</td>
<td>21</td>
<td>12</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>11</td>
<td>8</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>HRT use (Hormone replacement therapy)</td>
<td>4</td>
<td>2</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Age older than 40 years</td>
<td>20</td>
<td>9</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Low Parity (2 and less)</td>
<td>10</td>
<td>4</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Post-menopausal status</td>
<td>18</td>
<td>7</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0</td>
<td>1</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Table 4: Characteristics and comparison of patients having pre-cancer and cancer conditions.

Discussion

The Bethesda system was developed in 1988 to establish a common language in between the histopathologist and the gynecologist in diagnosing cellular atypia, on whether abnormal cells collected during pap smear screening test are squamous or glandular cytologically. Regarding the glandular type of abnormal cells, the diagnosis should be further refined to the site of their origin (endocervical or endometrial) in order to guide the clinician to minimize the potentially invasive further investigations. But unfortunately, it is not the case where the experience and inter–observer variation among cytopathologist are wide which makes it difficult to make the diagnosis highly sensitive and specific.

Our study focused on the incidence of AGUS in collected sample in our center, and to find a suitable guideline in approaching such patients in order to narrow the array of potential wide range of investigating procedures to reach to a solid diagnosis and not to miss potentially premalignant and malignant cases in our group of patients. The results showed a relatively higher incidence of AGUS (0.8%) compared to other studies reported in the literature (0.18–0.74%). This higher incidence might be attributed to two causes; firstly, the experience of our cytopathologist where the lack of experience is known to be a cause of low detection rate. Secondly, a good percentage of our study group patients were symptomatic and presented with a chief
complaint for which they underwent further investigations (46.7%) contrary to the routine checkup pap smears which were the main indications for this procedure in previously published studies which shows lower incidence.

Also, our study revealed serious disease whether premalignant or malignant in more than half of AGUS cases (52.9%), which is higher than the reported figures in other studies that did not exceed 50% [8-10] and two thirds of these confirmed to be cancerous and more than half of these cancers were endometrial adenocarcinoma. This high incidence of uterine origin malignancy might be attributed to the advanced mean age of the study sample though it was statistically insignificant in our study (48.2 years) as compared to the literature (17,18) which showed younger mean age of 45 years.

Colposcopy managed to diagnose 24% of our cancerous and precancerous lesions (12.9% and 11.3% respectively) where it is well known that squamous and glandular lesions are reported to co-exist in 5–40% of patients [8,18]; added to that, AGUS is relatively misleading to physicians where it predicts only 6–23% of glandular neoplasia in comparison to 36–77% in case of squamous neoplastic cells. [19]

Our data also identified three risk factors associated with the presence of malignant disease in patients with AGUS and these are: 1) age (older than 40 years), 2) presence of vaginal bleeding and 3) being menopausal. In addition to that there were less important risk factors such as smoking, low parity and use of hormonal replacement therapy. However, all these associations do not reach a statistical significance due to the small number of our study group. Despite that these associated factors might carry a clinical importance where their presence is to be considered a stronger indication for more aggressive investigations and undertaking multiple biopsies for those patients whose pap smear reports reveal AGCUS.

**Conclusion**

Though the incidence of AGUS is low, it is still important and clinically significant due to the high substantial risk of having underlying premalignant or malignant lesions. Thorough investigations should be performed to all these patients especially those having associated risk factors such as age above 40 years, menopause and abnormal vaginal discharge or bleeding.

**References**


