Correlation of KRAS Mutation with Mucinous Epithelial Lesions of the Endometrium: Implications for Biological Progression and Molecular Diagnosis

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ABSTRACT

Background: Mucinous epithelial changes are frequently encountered in endometrial biopsies. They may be classified into three morphologic categories (A, B and C) based on architectural complexity and cytological atypia to help predicting the risk of subsequent endometrial adenocarcinoma (EAC). KRAS mutations have been recently reported in atypical mucinous endometrial lesions and mucinous EAC. The aim of our study was to assess the prevalence and diagnostic and prognostic utility of KRAS mutation in the different morphological classes of mucinous endometrial changes.

Methods: Forty-six endometrial biopsies with mucinous change were retrieved from our departmental archives. All available H&E slides were reviewed and the cases were categorized into simple mucinous change without cytological atypia (Type A), complex mucinous epithelium without cytological atypia (Type B), and complex mucinous change with cytological atypia (Type C) or mucinous EAC.

RESULTS

Table 1. KRAS Mutation Status in Different Categories of Endometrial Mucinous Lesions

<table>
<thead>
<tr>
<th>Total No.</th>
<th>Average Age</th>
<th>Subtype</th>
<th>KRAS (+)</th>
<th>KRAS (-)</th>
<th>% KRAS (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>46</td>
<td>A</td>
<td>0</td>
<td>4</td>
<td>0.0%</td>
</tr>
<tr>
<td>22</td>
<td>40</td>
<td>B</td>
<td>13</td>
<td>9</td>
<td>59.1%</td>
</tr>
<tr>
<td>11</td>
<td>43</td>
<td>C</td>
<td>5</td>
<td>6</td>
<td>45.5%</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>Mucinous Carcinoma</td>
<td>6</td>
<td>1</td>
<td>85.7%</td>
</tr>
</tbody>
</table>

Table 2. Follow-up Hysteroscopy Results in Correlation with KRAS Mutation

<table>
<thead>
<tr>
<th>Total No.</th>
<th>Subtype</th>
<th>KRAS (+)</th>
<th>CAH/EAC</th>
<th>% CAH/EAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>0/1 (0.0%)</td>
<td>0/1</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>5/7 (71.4%)</td>
<td>4/7</td>
<td>57.1%</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>3/7 (42.9%)</td>
<td>5/7</td>
<td>71.4%</td>
</tr>
<tr>
<td>7</td>
<td>Mucinous Carcinoma</td>
<td>6/7 (85.7%)</td>
<td>7/7</td>
<td>100%</td>
</tr>
</tbody>
</table>

METHODS

• Retrospective test search for endometrial biopsy or curettage specimens with a final diagnosis of endometrial mucinous change or metaplasia and mucinous carcinoma from 1983 through 2011 was conducted.
• The original H&E slides of each case were reviewed and mucinous lesions were classified into the following four categories:
  • Simple mucinous change (Type A) is defined by the presence of linear or pseudostratiﬁed epithelial lining with minimal architectural complexity (mid epithelial tufting) and no or minimal cytological atypia (Figure 1-A).
  • Complex mucinous change (Type B) consists of mucinous epithelium with more extensive papillation, the presence of micromyoloid or cib保修 complex withﬁgu ﬁg ur with no or minimal cytological atypia (Figure 1-B).
  • Complex mucinous change (Type C) is defined as mucinous epithelium with either simple or increased architectural complexity along with the presence of moderate cytological atypia (Figure 1-C and D).
  • Mucinous adenocarcinoma was deﬁned by the presence of either endometrial adenocarcinoma with at least 50% of the tumor cells demonstrating intracytoplasmic mucin (Figure 1-E and F).
• KRAS mutation analysis was performed by polymerase chain reaction – single strand conformation polymorphism (PCR-SSCP, Figure 2).
• A total of 44 endometrial biopsies/curettage cases were included in the study and classiﬁed into Type A (4 cases), Type B (22 cases), Type C (11 cases) and mucinous adenocarcinoma (7 cases).
• KRAS analysis was informative in all (Table 1) and the mutation was detected in none (0/4) of Type A, 13/22 (60.9%) of Type B (Figure 2), 5/11 (45.5%) of Type C and 5/7 (71.4%) of mucinous carcinomas.
• Follow up specimens including both hysterectomy and endometrial biopsy or curettage were available in 35 cases with an average follow-up interval of 35.1 weeks. Benign endometrium was found in 2 Type A cases, CAH or EAC was found in 8 of 16 Type B cases (follow-up interval of 36.6 weeks) and 7 of 10 Type C lesions (follow-up interval of 40.2 weeks).
• When taking hysterectomy as the end point of follow up (Table 2), 37.1% of Type B (4/7) and 71.4% of Type C (5/7) cases were found to have CAH and/or EAC. In addition, 71.4% (5/7) of Type B cases and 42.9% (3/7) of Type C cases had KRAS mutation in their corresponding biopsy specimens.
• KRAS mutation has a positive predictive value (PPV) of 85.7% (7/8 analyzed, included 2 Type B and 5 Type C) and negative predictive value (NPV) of 66.7% (28/42) in mucinous lesions.

RESULTS

• Our data further emphasizes the architectural complexity as an important prognostic indicator for patients with mucinous endometrial lesions.
• Diagnostic separation of endometrial mucinous metaplasia into morphologically simple and complex categories constitutes a highly sensitive, although not specific, approach to assess the risk of development of precursor hyperplasia and endometrial adenocarcinoma.
• The presence of KRAS mutation in both mucinous adenocarcinoma and complex mucinous changes indicates that KRAS mutational activation is implicated in the pathogenesis of a significant subset of endometrial mucinous carcinoma.
• With a high positive predictive value, KRAS mutation analysis may offer an additional discriminatory power before risk stratification algorithm for patients with endometrial mucinous lesions. Additional studies are important to conﬁrm our findings.

CONCLUSIONS

Among various endometrial epithelial metaplasias, mucinous change is particularly relevant since it is frequently encountered in an endometrial biopsy of peri- or post-menopausal patients and is more likely associated with additional aggressive endometrial lesions. However, the frequent disparity between the cytological atypia and architectural alterations in a mucin lesion, especially in a small, fragmented biopsy may lead to signiﬁcant diagnostic challenges of interpretation to guide patient management. Type I endometrial adenocarcinomas frequently show mucinous differentiation, a subset of which are classiﬁed as mucinous adenocarcinomas. It has been hypothesized that subtypes of endometrial mucinous metaplasia are biologically related to endometrial adenocarcinoma as precursor lesions. Type II is a key oncogene in the EGF signaling cascade (RAS-MAPK pathway) and its mutation is an early oncogenic event in the development of human cancers. It is of particular interest that the presence of KRAS mutation correlates with mucinous differentiation in various human cancers including pancreas, colon, thyroid and lung cancer. KRAS is also frequently mutated in ovarian mucinous neoplasms and endometrial mucinous carcinomas. We systematically analyzed morphological categories of endometrial mucinous lesions in correlation with KRAS mutation status and clinical progression.

SELECTED REFERENCES