Adenoacanthoma of the endometrium: a separate entity or a histological curiosity?

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SUMMARY In a series of 42 patients with endometrial adenoacanthoma and of 53 with adenocarcinoma, age at the time of diagnosis, age at the onset of the menopause, gravidity, pathological staging, and survival were compared to see if there was any significant difference, apart from morphology, between the two tumours. No significant differences could be established, and it was concluded that adenoacanthoma should be regarded as a histological variant of adenocarcinoma and not as a separate entity.

Adenoacanthoma is a malignant epithelial tumour composed of both glandular and squamous elements. This was first described by Herxheimer in 1907 in gall bladder, stomach, caecum, pancreas, and parotid gland as well as in the endometrium. Since about 1940 it is principally the adenoacanthoma of the endometrium that has held the attention of pathologists. There is no agreement in the literature as to the frequency of this lesion; some reports regard the lesion as relatively rare, 2-6 while others record an incidence of about 30% of all endometrial malignancies.7-12

A similar discrepancy exists in the prognosis. In 1957, Novak and Nalley13 reported a case of endometrial adenoacanthoma and stated that the occurrence of squamous nests within an adenocarcinoma indicated a better prognosis than for an ordinary adenocarcinoma. Since then, a worse prognosis has been suggested 8 14-17 while others could establish no apparent difference between adenoacanthoma and adenocarcinoma. 9 12 18-21 The consensus now is that the two lesions have a similar prognosis.

Furthermore, there is no uniform definition of adenoacanthoma in the literature. Babid18 refers to a tumour in which there are 'acanthomatous elements intimately admixed with glandular carcinoma'. Pokoly10 defines it as an adenocarcinoma in which one nest of squamous epithelium can be found per 10 high-power fields. Woodington,21 on the other hand, specifies that the ratio of squamous to adenoid epithelium must be 1:30.

It was the object of this study to examine a series of patients with adenoacanthoma and to compare them with a similar group of patients with adenocarcinoma. The intention was to establish if there was an essential difference, apart from morphology, between the two tumours.

Material and methods

All patients who had been operated upon for a malignant tumour of the corpus uteri in the Wilhelmin Gasthuis, Amsterdam, between 1960 and 1969 inclusive were reviewed. All patients had undergone a vaginal hysterectomy after closure of the cervix over an alcohol-soaked swab. The patients were not irradiated either pre- or post-operatively.

The epithelial malignancies were reclassified into adenocarcinoma, clear cell carcinoma, and adenoacanthoma. As has already been pointed out, there are varying definitions in the literature as to what precisely constitutes an adenoacanthoma. Since the only characteristic feature of this lesion is squamous epithelium contiguous with adenocarcinoma it was decided that all tumours containing unmistakable squamous epithelium intimately admixed with glandular carcinoma would be classified as adenoacanthoma, irrespective of the quantity of that squamous epithelium.

From the total patient material 95 cases were selected for further study on the basis of the adequacy of the clinical and pathological documentation. Documentation was considered to be adequate in those patients in whom staging of the tumour could be accurately assessed and who had been followed up for at least five years.

The following classification was used: stage 0, superficial tumour growth without myometrial

1064
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invasion and confined to the body of the uterus; stage IA, invasion of the myometrium—less than half the full thickness of the myometrium invaded; stage IB, invasion of the myometrium—more than half the full thickness of the myometrium invaded; stage II, invasion of the cervix; stage III, tumour present outside the uterus but confined to the true pelvis; stage IV, distant metastases and/or invasion of bladder and/or rectum.

A limited number of clinical details was also considered, namely, age of patient at the time of diagnosis, age at onset of the menopause, number of pregnancies, and survival. The selected cases of adenocarcinoma and adenoacanthoma were then compared on the basis of these data.

Results

Altogether 149 patients were operated upon for an epithelial malignancy of the corpus uteri during the 10-year period beginning in 1960. Of these patients, 96 (65·8%) had an adenocarcinoma, 5 (3·3%) had a clear cell carcinoma, and 46 (31·9%) had an adenoacanthoma.

Of the 149 patients, 53 with adenocarcinoma, one of which showed the features of a clear cell carcinoma, and 42 with adenoacanthoma were considered to be adequately documented and were selected for further study. The results are summarised in the Table. There were no stage IV cases among the selected patients of either group. The total survival of the pure adenocarcinoma group, defined as tumour-free after five years or dead after not less than three years without tumour, was 83%, while the total survival for the adenoacanthoma group was 78·6%. The survival figures for the individual stages are given in the Table.

Discussion

Adenoacanthoma of the body of the uterus is a tumour surrounded by confusion. There is no adequate estimate of its frequency, there is still some disagreement with regard to prognosis, and, furthermore, there is no uniformly accepted definition of what precisely constitutes the lesion. This point readily explains the great variation in the reported frequency of the tumour.

The definition used in the present series is less strict than others whereby a moderately large percentage of tumours was classified as adenoacanthoma. Even so, the incidence in this study corresponds with that of other workers.11 14 If those tumours in this series that fulfil the definition of Pokoly are selected, the incidence falls to 15%, which is lower than the 23·9% found by Pokoly, but other factors remain similar to those of the original adenoacanthoma group. The rather generous

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High-power detail of a focus of squamous metaplasia within an adenoacanthoma (Haematoxylin and eosin × 140).
A comparison between adenocarcinoma and adenoacanthoma with regard to pathological staging and survival

<table>
<thead>
<tr>
<th></th>
<th>Adenocarcinoma</th>
<th>Adenoacanthoma</th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>53</td>
<td>42</td>
</tr>
<tr>
<td>No. premenopausal</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Mean age at menopause (yr)</td>
<td>48 (SD 5-4)</td>
<td>49·3 (SD 4-1)</td>
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<tr>
<td>Mean age at diagnosis (yr)</td>
<td>60·6 (SD 8-3)</td>
<td>63·2 (SD 9-0)</td>
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<tr>
<td>Mean no. of pregnancies</td>
<td>2·2 (SD 2-2)</td>
<td>2·6 (SD 2-3)</td>
</tr>
<tr>
<td>Percentage nulliparous patients</td>
<td>22-6</td>
<td>16·7</td>
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</table>

**Stage I**

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<thead>
<tr>
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<th>No. of patients</th>
<th>Percentage of total</th>
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<tr>
<td>No. of patients</td>
<td>7</td>
<td>6</td>
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<tr>
<td>Percentage of total</td>
<td>13·2</td>
<td>14·3</td>
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<tr>
<td>No. premenopausal</td>
<td>3</td>
<td>1</td>
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<td>Mean age at menopause (yr)</td>
<td>40·0 (SD 6-1)</td>
<td>51·4 (SD 2-9)</td>
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<tr>
<td>Mean age at diagnosis (yr)</td>
<td>52·3 (SD 3-1)</td>
<td>59·5 (SD 7-5)</td>
</tr>
<tr>
<td>Mean no. of pregnancies</td>
<td>2·1 (SD 1-3)</td>
<td>3·2 (SD 1-6)</td>
</tr>
<tr>
<td>% survival</td>
<td>100</td>
<td>100</td>
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**Stage IB**

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<tr>
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<th>Percentage of total</th>
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<tr>
<td>No. of patients</td>
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<td>9</td>
</tr>
<tr>
<td>Percentage of total</td>
<td>17·0</td>
<td>21·4</td>
</tr>
<tr>
<td>No. premenopausal</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Mean age at menopause (yr)</td>
<td>47·5 (SD 5-3)</td>
<td>47·1 (SD 4-3)</td>
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<tr>
<td>Mean age at diagnosis (yr)</td>
<td>60·4 (SD 5-5)</td>
<td>67·8 (SD 7-1)</td>
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<tr>
<td>Mean no. of pregnancies</td>
<td>1·9 (SD 2-4)</td>
<td>2·8 (SD 2-2)</td>
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<tr>
<td>% survival</td>
<td>88</td>
<td>77·8</td>
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**Stages II and III**

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<th>No. of patients</th>
<th>Percentage of total</th>
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<tr>
<td>No. of patients</td>
<td>10</td>
<td>4</td>
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<tr>
<td>Percentage of total</td>
<td>18·9</td>
<td>9·5</td>
</tr>
<tr>
<td>No. premenopausal</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Mean age at menopause (yr)</td>
<td>47·9 (SD 6-3)</td>
<td>49·0 (SD 5-0)</td>
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<tr>
<td>Mean age at diagnosis (yr)</td>
<td>64·1 (SD 12·1)</td>
<td>64·0 (SD 11-0)</td>
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<tr>
<td>Mean no. of pregnancies</td>
<td>1·9 (SD 1-1)</td>
<td>2·5 (SD 2-6)</td>
</tr>
<tr>
<td>% survival</td>
<td>40</td>
<td>0</td>
</tr>
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</table>

The mean ages at onset of the menopause and at differentiation, and tumours arising from them are gradually being recognised. Since the cervix and the endometrium both arise from Müllerian epithelium, similar cells might be expected to be present in the endometrium, but, as yet, no one has been able to demonstrate their existence.

A more acceptable theory is that the squamous epithelium arises by metaplasia of the tumorous glandular epithelium.12-14 29 This theory would explain the localisation of the squamous nests deep down in the tumour. Furthermore, a diligent search will sometimes reveal transitional zones between the two epithelial types, such as was described by Tweedale et al.12

The consequences of this theory are of vital importance in understanding the nature of adenocarcinoma, for it follows that the squamous epithelium has arisen directly from malignant epithelial cells and therefore must itself be malignant, however benign it may appear histologically. It further follows that the mixed or adenosquamous carcinoma is simply an adenoacanthoma in which the squamous component reveals its inherent malignancy. It is not, therefore, an entity apart but a less well differentiated variant of adenoacanthoma.

It must now be considered how the metaplasia takes place. During the course of the present study we noticed that in about 80% of adenoacanthomas inflammatory infiltrate was present and that in approximately 35% this was quite dense. Only 60% of the pure adenocarcinomas were associated with inflammation, the infiltrate being dense in approximately 20%. It is possible, therefore, that the metaplasia takes place, at least in part, as a result of inflammatory irritation.

Squamous metaplasia within an adenocarcinoma appears to have a modal distribution whereby some tumours undergo spontaneous metaplasia while others do not, even in the presence of severe inflammation. Between these two extremes there is a wide range of tumours whose metaplastic response to inflammation is extremely variable.

The question then arises whether this metaplastic change indeed identifies a separate entity, or merely represents a histological variant of adenocarcinoma which is of no further clinical significance.

The results presented in this study reveal no significant differences between the two lesions. With the exception of stage II and stage III tumours, the prognosis was similar, the small differences being no more than could be expected to occur by chance. The difference in stages II and III can be explained by the very small numbers involved. Furthermore, the distribution of staging was similar in both tumours.

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The mean ages at onset of the menopause and at...
the time of diagnosis showed no statistically significant differences between the two groups, nor did the mean gravidity values.

We conclude, therefore, that adenocanthoma does not differ significantly from adenocarcinoma in clinical presentation or biological behaviour and that it should be regarded as a histological variant of adenocarcinoma and not as a separate entity.

References

1 Hersheimer G. Uber heterologe Cancroide. Beitr Pathol 1907;41:348-412.

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