ENDOMETRIAL CARCINOMA AND ITS PRECANCEROUS LESIONS RELATED WITH GLANDULAR CYSTIC HYPERPLASIA

Yoshiharu TSUKAHARA, Yoshihito FUKAMATSU and Toru FUKUTA
Department of Obstetrics and Gynecology, Shinshu University School of Medicine, Matsumoto

Synopsis  Morphological investigations were carried out on 184 cases with GCH and related diseases, and the following results were obtained:
1. Pure GCH was observed in 112 cases (60.9%), GCH with ADH in 56 cases (30.4%), and GCH with ATH in 11 cases (6.0%). ECA related with GCH was found in 5 cases (2.7%).
2. It was suggested that GCH can serve as a remote precursor of ECA. Namely, GCH in some cases was found to develop into ECA apparently through the change from ADH to ATH.
3. It was morphologically observed that in GCH, both glandular epithelium and stromal cells were proliferated by being stimulated by estrogen, and such a proliferation was interrupted by an estrogen antagonist, progesterone. On the other hand, in the case of ATH, the growth of stroma was generally decreased and the proliferation of glandular epithelium became predominant. Moreover, the action of progesterone was minimum in ADH and ATH. These findings indicate that precancerous lesions such as ADH and ATH are those capable of developing easily into carcinoma.

Key words:  Endometrial carcinoma • Precancerous lesions • Glandular cystic hyperplasia

Introduction

The process of development from glandular cystic hyperplasia (GCH) to endometrial carcinoma (ECA) has not been fully clarified yet. However, it has been occasionally reported that GCH developed into ECA after several years.

Atypical hyperplasia (ATH), which is thought to be a precursor of ECA, has also been reported to progress from GCH in some cases. The nomenclature and the histological criteria for this ATH, however, have not been established yet, thus each investigator is using different names. For instance, Müller and Keller, and Laszloet al. called it ATH, and Gusberg reported the name of adenomatous hyperplasia (ADH), and Hertig and Sommers used the name of adenocarcinoma in situ (AIS), while Hall has adopted the term irregular hyperplasia.

Although there is no report giving direct evidence of the transformation from ATH to ECA, the existence at high frequency of GCH and ATH in the noncarcinomatous region which is around ECA but not manifested with cancer yet has been reported. Therefore, it may be said that GCH and ATH are playing a significant role as precancerous lesions.

Only a few reports have been published regarding the cases in which both GCH and ADH or both GCH and ATH coexist together. In the present study, we have carried out pathomorphological investigations on ADH and ATH which were related with GCH, and examined the significance of GCH and these precancerous lesions in carcinogenesis.

Materials and Methods

1. Cases
One hundred and eighty four cases which had been diagnosed as GCH by the D & C performed at our department and related hospitals since 1975 were subjected to the present study. These cases consisted of those having morphologically pure GCH, those with GCH together with ADH or ATH, and those having ECA in addition to these precursor lesions.

2. Histological criteria
The cases were classified into 4 groups according to the degree of proliferation and of atypism: 1) GCH, 2) GCH with ADH, 3) GCH with ATH, and 4) ECA related with the GCH. The histological criteria used for these groups are shown in Table 1.
May 1983  ENDOMETRIAL PRECURSOR LESIONS RELATED WITH GCH  707

Table 1. Histological criteria of GCH, adenomatous hyperplasia, atypical hyperplasia, and endometrial carcinoma

<table>
<thead>
<tr>
<th></th>
<th>GCH</th>
<th>Adenomatous hyperplasia</th>
<th>Atypical hyperplasia</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic change</td>
<td>*</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Crowding</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Irregular profile of glands</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Pale or eosinophilic cytoplasm</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Stratification</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Loss of polarity</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Anisokaryosis</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Irregular nuclear profile</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Large vesicular nucleus</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tufting</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Bridging</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Gland-in gland</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>

(±: mild, +: moderate, *: marked)

with and without ADH or ATH, the generally postulated concept that GCH develops into ADH, then into ATH and finally progresses to ECA.

Results

I. Morphology
A. GCH

The endometrium was markedly hypertrophic, glands were dilated in a cystic form showing a Swiss-cheese pattern. The margin of the gland was smooth without showing irregularity (Fig. 1). The glandular epithelium generally showed a slight degree of stratification and mitosis. Stromal cells showed strong proliferation, and were occasionally accompanied by foam cells. Secretory changes in the glandular epithelium and stromal cells were also noted in some cases.

B. GCH with ADH

Some of cystically dilated glands had irregular infoldings, and the adenomatous growth of small satellite glands was observed around such glands (Fig. 2). These satellite glands were crowded

Fig. 2. Adenoma-like proliferation of glands surrounding the cystic lesions, ×20

Fig. 3. Slightly crowded hyperplastic glands adjacent to the cystic lesions, ×20
together, and surrounded with narrow stroma. The atypism of the glandular epithelium was mild, and structural abnormalities of the glands were usually absent (Fig. 3).

C. GCH with ATH

The crowding of the glands became very conspicuous (Fig. 4). The tufting or bridging of the epithelium towards the glandular cavity were observed (Fig. 5), and the gland-in-gland pattern was also occasionally noted. The cytoplasm was pale or eosinophilic, and had a large vesicular nucleus (Fig. 6). Nuclei were somewhat irregular in size and shape, and a mild loss of polarity was also observed. Glandular cystic patterns decreased in number, and foam cells became pronounced, while stromal hyperplasia generally decreased. The foam cell contained lipid, but was devoid of glycogen and mucin (Fig. 7). Glandular epithelium frequently showed strong stratification.

Fig. 4. Marked crowded glands having narrow stroma, ×200

Fig. 5. A slight structural atypism of intraglandular tufting or gland-in-gland, ×40

Fig. 6. Atypical cells with vesicular nuclei and eosinophilic cytoplasm, ×400

Fig. 7. Numerous foam cells in the endometrial stroma, ×200

Fig. 8. Highly proliferated glands with complicated structures, ×40

D. ECA related with GCH

The degree of proliferation and of the crowding of the glands became extremely intense, and marked irregularity and complicated structures were seen in the gland (Fig. 8). Size and shape var-
Fig. 9. Marked nuclear proliferation with loss of polarity, × 400

Fig. 10. Structural abnormalities showing bridging and gland-in-gland pattern, × 100

Fig. 11. Transitional image in cystically dilated glands between benign and malignant portion, × 40

The number of foam cells were found to be less frequent in cases with GCH than in those with GCH with ADH, while secretory changes were more frequent in the former cases.

IV. Clinical aspects of cases with ATH and ECA

Tables 4 and 5 show the clinical aspects of 11 cases with ATH and 5 cases having ECA. Surgical operations were carried out in 7 out of the 11 cases for the purpose of treating ATH. None of them, however, showed ECA in their surgical specimens. Four cases with no surgical operation are under follow-up at present, and one of them exhibited atrophic endometrium in a recently performed D & C, the ATH which was observed 5 years ago was not detected at this time.

The ECA which was thought to have been

Table 2. Incidence of GCH and its related lesions

<table>
<thead>
<tr>
<th>Case</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCH</td>
<td>112</td>
</tr>
<tr>
<td>GCH with adenomatous hyperplasia</td>
<td>56</td>
</tr>
<tr>
<td>GCH with atypical hyperplasia</td>
<td>11</td>
</tr>
<tr>
<td>Adenocarcinoma related with GCH</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>184</strong></td>
</tr>
</tbody>
</table>

Table 3. Incidence of foam cell and secretory changes in GCH and adenomatous hyperplasia related with GCH

<table>
<thead>
<tr>
<th></th>
<th>GCH n=112</th>
<th>ADH related with GCH n=56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foam cell</td>
<td>8 (7.1%)</td>
<td>21 (37.5%)</td>
</tr>
<tr>
<td>Secretory change</td>
<td>54 (48.2%)</td>
<td>18 (32.1%)</td>
</tr>
</tbody>
</table>
developed from GCH was seen in 5 of the cases. Surgical operations were performed for all of these cases, and they were all early cases. Four out of these 5 cases showed ovarian cortical hyperplasia.

**Discussion**

It is common to encounter cases of ECA having a GCH lesion. For instance, Gray et al.\(^5\) reported that 46.3% of ECA cases showed GCH in the noncancerous endometrium, and Hertig & Sommers\(^6\) also observed such a change in about half of the cases they studied.

GCH is generally accepted as a remote precursor of ECA\(^13\), and its percentage of incidence has been reported as 6.8% by Kofier\(^19\), 6.0% by Sommers\(^19\), 5.0% by Ober, 4.2% by Rigo, and 2.0% by Hall\(^8\). McBride\(^13\), on the other hand, reported a value of only 0.4%, and stated that GCH might not be a precursor of ECA.

It is extremely difficult to accurately know the duration required for the development of ECA from GCH. This is in contrast to the present situation of the cervical cancer of the uterus, in which the natural history from a precancerous state to carcinoma has been clarified to a great extent.

The periods required for carcinogenesis reported in literature are as follows: 6–13 years from GCH to ECA, 1–5 years from GCH to ATH, and 3–5 years from ATH to ECA\(^9\), 12 years from ATH to ECA in premenopause cases and 6 years in postmenopause cases\(^1\), and 4–14 years from ATH to ECA\(^1\).

WHO\(^8\) classified endometrial lesions at precancerous states into cystic hyperplasia, adenomatous hyperplasia and atypical hyperplasia. These
names, however, are not consistently used by every investigator, and the criteria are also not firmly established. The atypical hyperplasia defined by WHO in particular corresponds to the carcinoma in situ termed by Hertig & Sommers\(^9\) and also to the marked adenomatous hyperplasia by Gusberg\(^8\).

Except for GCH, both ADH and ATH are difficult to be distinguished from well-differentiated adenocarcinoma from a pathomorphological point of view. It is also not fully clarified what morphological images reflect a course to irreversible carcinogenesis. Therefore, unlike the common use of the term, CIS, for uterine cervical cancer, the term, AIS, has not been employed by many investigators in the case of endometrial carcinoma. Furthermore, it is also known that the cases which were pathologically diagnosed as AIS or ATH do not always take a course to malignancy. For example, the percentage of transformation to malignancy has been reported to be less than 8% by Gusberg\(^8\), 6% by Hall\(^9\) and 6% by Sommers\(^10\). Thus, the percentage of transformation to malignancy is smaller than 10% in general. The fact that a conversion to benign is even observed in some cases makes the independency of AIS to be more unlikely.

Further possible reasons for the difficulty of establishing the independency of AIS are as follows: 1) the natural history of the precancerous state in the endometrium is difficult to be clarified, 2) stromal invasion is difficult to be confirmed histologically, 3) hormones, particularly progesterone, cause morphological changes in the glandular epithelium\(^10\).

According to electron microscopic observations made by Ferenezy\(^11\), AIS was shown to be an immediate precursor of invasive carcinoma, rather than ADH, but morphological distinction between ADH to AIS could not be obtained.

The developmental process from GCH to ADH and to ATH seems to have been confirmed by the findings in some cases of the present study. Namely, ADH was related with GCH in 30.4% of the cases studied, and ATH was accompanied by GCH in 6.0% of the cases. Moreover, the development of ECA from GCH was observed in 5 cases (2.7%). One of such cases was a young (25 yr old) woman. Regarding this point, Sommers et al.\(^18\) also reported that 5 out of the 16 young patients with ECA showed the existence of GCH as a precursor.

That GCH and ADH are induced by hyperestrogenism has been accepted by many investigators\(^11\) including Gusberg\(^6\), and Hertig & Sommers\(^9\). Evidence for the genesis of such lesions by the morrbific action of estrogen are as follows: 1) the foam cell which is thought to be induced by action of the excessive estrogen is observed to be present in abundance in GCH and ATH\(^9\); 2) ovarian stromal hyperplasia is frequently accompanied with GCH. In this connection, Stearns et al.\(^20\) stated that 70.7% of GCH was associated with ovarian stromal hyperplasia; 3) the hyperthecosis of the ovary may suppress the ruptu- of the ripening follicles, induce the long period of the anovulatory cycle, and prolong the estrogen action; and 4) granulosa cell tumors are frequently associated with ECA.

Although the majority of GCH does not serve as a direct cause of ECA, it cannot be denied that GCH is a remote cause of ECA. This may be the result of the following findings: 1) As a result of the prolonged action of estrogen, the glandular epithelium shows an abnormal growth, and irreversible, autonomous proliferation may be finally induced. 2) Even after the menopause, the stromal hyperplasia of the ovary continues to exist, thus stimulation by estrogen continues. 3) A GCH lesion does not undergo complete shedding but remains in a portion of the endometrium, as a polyp-like lesion, for a long period of time. Such a portion may transform to a carcinoma some years later.

However, carcinogenesis may not be taken place only by the prolonged action of the estrogen or by excessive amount of estrogen. Therefore, the presence of other unknown factors are naturally postulated by many investigators.

In the clinical management of GCH, we think that the follow-up should be performed on the basis of recognition that GCH is a remote cause of ECA, and is one of the high risk factors to ECA. Moreover, the diagnostic standard for ADH or ATH is needed and it is hoped that it will be established in the very near future.

References

概要 文献的にみて GCH と ADH あるいは GCH と ATH との共存例について研究した報告は少ない。今回、GCH に合併して認められた ADH, ATH および ECA について病理形態学的に検討し、GCH 及びこれら前癌性病変が癌発生過程の上で如何なる意義を有するかについても考察した。得られた成績は以下の如くである。

1. 184例の GCH 及びこれと関連する疾患のうち、純粋な GCH は112例（60.9％）、GCH に ADH を伴うものが56例（30.4％）、GCH に ATH を伴うものが11例（6.0％）にみられた。更に GCH を基盤として発生したと考えられる ECA が5例（2.7％）に認められた。

2. GCH は ECA の remote precursor となりうることが示唆された。即ち GCH から ADH, 更に ATH の過程を経て ECA へ進展したと思われる症例の頻度は上述の如く、段階的に減少し、かつ各々の間に移行像が認められた。

3. GCH 及び一部の ADH では腺上皮及び間質細胞の両者が増生し、しばしば secretory change の像を認めた。一方、ATH では一般に間質の増生が低下し、腺上皮の増生が主となり、腺上皮や間質細胞における secretory change も著しく強化した。この事実はこれら前癌性病変が ECA へ発展し易い状況であることを示すものである。