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Indicators of proliferative activity of endometrium in women with immunodeficiency

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ABSTRACT

To investigate proliferation in disease free postmenopausal endometrium and that harbouring endometrial adenocarcinoma—is there a dynamic, yet lurking, potential for atrophic endometrium to give rise to endometrial adenocarcinoma? The study comprised 84 disease free endometria from asymptomatic postmenopausal women who had undergone hysterectomy for prolapse, and 50 endometrioid cell type endometrial adenocarcinomas with adjacent uninvolved postmenopausal endometrium. The non-neoplastic tissues were separated histologically into active, inactive, and mixed forms, although only the first two categories were studied immunohistochemically for oestrogen and progesterone receptors (ERs, PRs), epidermal growth factor receptor (EGFR), Ki-67, and angiogenic activity. All postmenopausal endometria were atrophic, but only 42 were inactive; of the remaining samples, 22 were weakly proliferative and 20 were mixed active and inactive. In contrast, the nonneoplastic component of 43 of the 50 endometrial adenocarcinomas examined was of the active form; four specimens were of the pure and 39 of the mixed form. Interestingly, high ER and PR expression was seen in active and inactive endometria, but only the former were EGFR positive and had high proliferative (Ki-67) and angiogenic activity. A similar trend was also shown by the non-neoplastic atrophic endometrium adjacent to endometrial adenocarcinoma. At least half of the disease free postmenopausal atrophic endometria show a weak proliferative pattern, either diffuse or focal, probably as a response to continuous low level oestrogenic stimulation. These tissues have a latent, although very small, carcinogenic potential, as demonstrated by the immunohistochemical profile and their frequent association with adjacent endometrial adenocarcinoma.

1. Introduction

The endometrium, a tissue of continuously changing patterns and immense proliferative activity during a woman's reproductive life, becomes atrophic after the menopause as a result of ovarian failure. At this time there is loss of the functional layer and the endometrial glands take on a simple tubular, often cystic form,

showing neither proliferative nor secretory activity, whereas the endometrial stroma turns fibrous [1]. ‘‘Excessive and unopposed oestrogenic stimulation is not uncommon after the menopause’’ It may appear paradoxical, but it is against this background of atrophy that most endometrial adenocarcinomas develop, and only 15–20% of them arise from a hyperplastic endometrium [2] indicating that excessive and unopposed oestrogenic stimulation is not uncommon after the menopause. There is also a hitherto unspecified proportion of postmenopausal endometria which, despite being atrophic, retain a weak proliferative pattern for many years [1], [3], [4] probably as a response to continuous low level oestrogenic stimulation. What is the share, if any, of these uterine mucosae in the genesis of endometrial adenocarcinoma? Are these at a higher risk of progression than others or are these only capable, among atrophic endometria, of giving rise to malignant disease? Our study was designed to explore the above questions, in parallel with examining the frequency of the various postmenopausal endometrial patterns and their immunohistochemical profile.

2. Methods

The material used in our study comprised 134 endometrial tissues, of which 84 were collected from asymptomatic postmenopausal women undergoing hysterectomy for a prolapsed uterus, and 50 from patients with endometrial adenocarcinoma, of the well differentiated endometrioid cell type. The selection criteria for admission into the study were: (1) cessation of menstruation for at least five years; (2) absence of hormonal treatment or irradiation during the menopause; (3) absence of gynaecological symptoms (for the patients without cancer only); and (4) at least three haematoxylin and eosin (H&E) sections available for evaluation of the nonneoplastic endometrium.

3. Discussion

The message that emerged from our study is clear and simple: endometrial adenocarcinomas related to endometrial atrophy (as most of these tumours are) originate from weakly proliferating glands, not from a background of endometrial inertia. This is not a paradox, because endometria showing weak proliferative activity are not uncommon after the menopause [1] and, indeed, more than half of the atrophic, disease free, symptom free postmenopausal endometria in our series exhibited such activity, either in a diffuse or focal fashion. Earlier, Archer and colleagues [3], [4] investigating endometrial patterns in asymptomatic postmenopausal women, found a similar proliferative activity in approximately 25% of the cases studied and hyperplastic disease in less than 5%, despite using biopsy and curettage specimens rather than hysterectomy samples. It is probable that the presence of a weak proliferative pattern in a postmenopausal atrophic endometrium is a response of the uterine mucosa to continuous low level oestrogenic stimulation. This is in accord with the reported increased ability of postmenopausal women to convert androstenedione, mainly of adrenal origin, into oestrone in the adipose tissues of the body using the enzyme aromatase (peripheral aromatisation) [9– 11]. The conversion increases with increasing body weight (increased numbers of fat cells) and with advanced age (increased specific activity of aromatase)11; the factors of aging and obesity, both of which are common in patients with endometrial cancer, appear to be additive [12]. Interestingly, oestrone is the most important oestrogen in endometrial carcinogenesis [13].

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