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II.8 Significance of Benign Uterine Pathology on Tamoxifen

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PROLONGED TAMOXIFEN therapy is associated with proliferative endometrial abnormalities such as hyperplasia, polyps and malignant neoplasms [1, 2]. Pathological examination of these lesions gives important clues as to the relationship between the benign and malignant lesions. Tamoxifen-associated endometrial hyperplasia is characterised by grossly visible endometrial thickening. Microscopically, the endometrial stroma is relatively paucicellular and conspicuously fibrotic. Many endometrial glands are cystically dilated but some show architectural distortion and there may be focal glandular crowding. The epithelial cells show mitotic activity and epithelial metaplasias similar to those seen in tamoxifen-associated endometrial polyps [3]. Tamoxifen-associated endometrial polyps are unusually large and often multiple [3–5]. Most develop on a background of endometrial hyperplasia [5]. Microscopically, they are composed of distorted glands surrounded by abundant fibrotic or myxoid connective tissue with patchy periglandular condensation of stromal cells. Mitotic activity is seen in both the stromal and epithelial cells. The epithelial cells show a variety of epithelial metaplasias. This combination of mitotic activity, epithelial metaplasias and patchy periglandular stromal condensation is very suggestive of a tamoxifen-associated polyp [5].

The significance of the stromal alterations found in tamoxifen-associated endometrial hyperplasia and polyps is uncertain. However, experimental evidence suggests that endometrial epithelial proliferation is mediated by endometrial stroma [6] and that stromal fibroblasts induce epithelial metaplasia [7]. In the light of these findings, tamoxifen-associated endometrial stromal alterations may be important in mediating endometrial epithelial growth, polypogenesis and the endometrial epithelial metaplasias seen in tamoxifen-associated endometrial polyps.

The epithelial metaplasias seen in tamoxifen-associated endometrial polyps and hyperplasia are of particular interest in the context of carcinogenesis. Metaplasia is a pathological term meaning altered differentiation. It has been regarded as a benign process which occurs as a physiological response to injury. However, there is an important link between metaplasia and neoplasia.

Metaplasias in the stomach and oesophagus are strongly implicated in carcinogenesis. In the stomach, epidemiological and pathological studies have repeatedly demonstrated an association between intestinal metaplasia and gastric adenocarcinoma [8]. The increased risk of gastric cancer is proportional to the extent of the metaplasia. Barrett's oesophagus is a condition in which the normal oesophageal squamous epithelium is replaced by metaplastic gastric and/or intestinal epithelium. It is associated with an increased risk of dysplasia and oesophageal adenocarcinoma [9]. In keeping with these observations, molecular pathological studies have found telomere reduction, oncogene and tumour suppressor gene mutations and micro-satellite instability in intestinal metaplasia of stomach [10]. Tumour suppressor gene mutations have also been reported as occurring in Barrett's oesophagus [11].

It is therefore not surprising that tamoxifen-associated endometrial polyps are characterised not only by epithelial metaplasias but also by a high prevalence of focal endometrial carcinoma arising within the polyps [3, 5]. This phenomenon is extremely uncommon in the general population.

Thus, there is a spectrum of overlapping pathological findings in tamoxifen-treated endometria. These range from simple endometrial hyperplasia to endometrial cancer. The intervening ground is occupied by endometrial polyps with conspicuous epithelial metaplasias which arise on a background of hyperplasia, and endometrial cancers which arise in these polyps. This overlapping spectrum of pathological findings suggests that endometrial hyperplasia is an important precursor of endometrial polyps and that endometrial polyps themselves represent an intermediate step in the development of endometrial carcinoma, at least in the context of tamoxifen therapy.

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