Mammary Gland – Hyperplasia

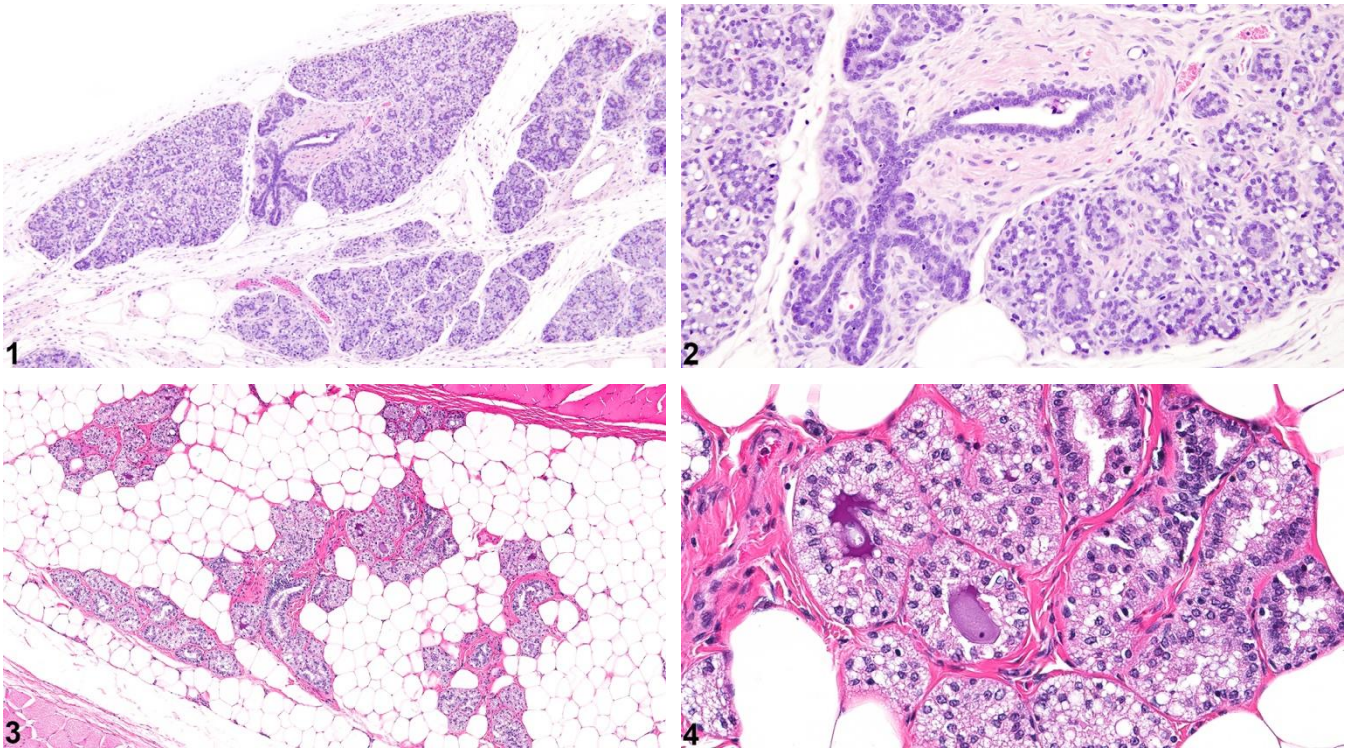

Figure Legend: Figure 1 Mammary gland - Hyperplasia, Lobular in a female F344/N rat from a chronic study. There are multiple enlarged lobules with increased numbers of alveoli in the mammary gland. **Figure 2** Mammary gland - Hyperplasia, Lobular in a female F344/N rat from a chronic study (higher magnification of Figure 1). Enlarged lobules with increased numbers of alveoli in the mammary gland. **Figure 3** Mammary gland - Hyperplasia in a female F344/N rat from a subchronic study. The mammary gland has a “masculinized” appearance (lobuloalveolar morphology similar to that in control males). **Figure 4** Mammary gland - Hyperplasia in a female F344/N rat dosed with an anabolic steroid in a subchronic study (higher magnification of Figure 3). There is a lobuloalveolar pattern to the female mammary gland rather than the normal tubuloalveolar pattern.

Keywords: mouse; rat; mammary gland; duct; alveolus; hyperplasia; lobular; atypical

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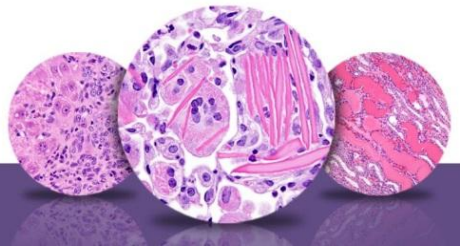
Comment: Normally, the greatest degree of mammary gland proliferation and secretory activity in female rats and mice results from pregnancy and lactation; similar changes can also occur in pseudopregnant females. Physiological mammary gland proliferation can also exhibit some variation depending on the stage of the estrous cycle, with most available studies reporting the most prominent lobular and alveolar development in metestrus and early diestrus.

Nonphysiological, spontaneously occurring mammary gland hyperplasia of uncertain etiology is a common aging change in virgin rats and mice, and can occur in both sexes. Mammary gland hyperplasia can also result from ovarian or pituitary hormone imbalances, which can be primarily or secondarily induced by factors such as exogenous toxins and nutrient deficiencies. Hyperplasia can also be a precursor to mammary gland neoplasia (spontaneous or treatment-related). *Lobular hyperplasia* (Figure 1 and Figure 2) can be focal or diffuse and is characterized by enlarged lobules with increased numbers of relatively normal alveoli. Ducts are typically not affected. Depending on the amount of intraluminal secretions, the affected alveoli may have a variable diameter but are lined by a single layer of well-differentiated cells. Reactive fibrous stroma is usually present, with amounts ranging from rather scanty to more extensive. However, the lack of both compression and a prominent collagenous stroma are features that distinguish lobular hyperplasia from fibroadenoma. As well as being a treatment-related or aging change, lobular hyperplasia in females can be a physiological change occurring during pregnancy and lactation, a result of xenobiotics that cause hyperprolactinemia, as well as in pseudopregnant animals. Lobular (alveolar) hyperplasia may be a precursor of adenoma, fibroadenoma, or adenocarcinoma. However, chemically induced hyperplastic lobules do not appear to be precursors to adenocarcinoma.

Male mice and rats normally have abundant mammary gland tissue, which can also undergo spontaneous or treatment-related hyperplasia. Unlike mice and other species, the mammary glands of rats exhibit sexual dimorphism, with glands in non-pregnant and non-lactating females having a tubuloalveolar morphology, while males exhibit a lobuloalveolar appearance. Thus, administration of certain agents (androgens, anabolic steroids, etc.) to female rats can result in the alteration of the mammary gland morphology to the typical male-like lobuloalveolar



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morphology ("masculinization" or "virilization"). Figure 3 and Figure 4 illustrate the mammary gland with a lobulolalveolar pattern (similar to that in control males) from a female rat dosed with oxymetholone (an anabolic steroid) for 13 weeks; the appearance is quite different from the usual female tubuloalveolar morphology observed in control female rats from the same study.

Conversely, administration of other agents (estrogens, prolactin, compounds such as dopaminergic receptor antagonists that indirectly result in hyperprolactinemia, etc.) can result not only in mammary gland hyperplasia in male and female rats, but also in female-like tubuloalveolar mammary gland morphology ("feminization") in male rats.

Recommendation: Mammary gland hyperplasia should be diagnosed and assigned a severity grade when it is considered treatment related. If pertinent, appropriate modifiers (lobular, focal, diffuse, etc.) should be included in the diagnosis. Evaluation of mammary glands in females should take into account the concurrent stage of the estrous cycle, and the possible presence of pregnancy or pseudopregnancy, in which case they should not be diagnosed but should be discussed in the pathology narrative. If a significant number of the hyperplastic cells have atypical features, then Mammary gland - Atypical Hyperplasia should be diagnosed (see Mammary gland - Atypical Hyperplasia).

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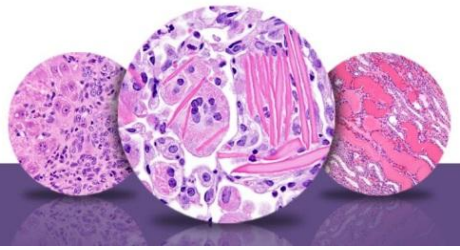

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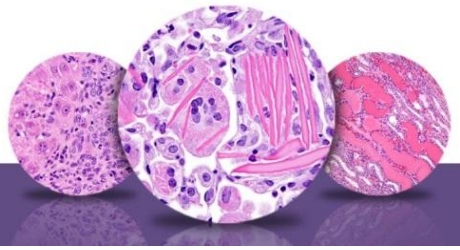

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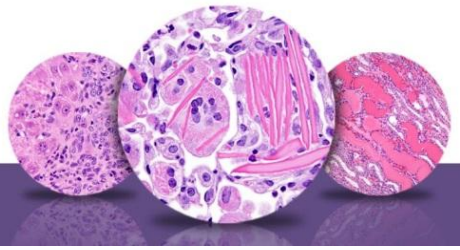

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