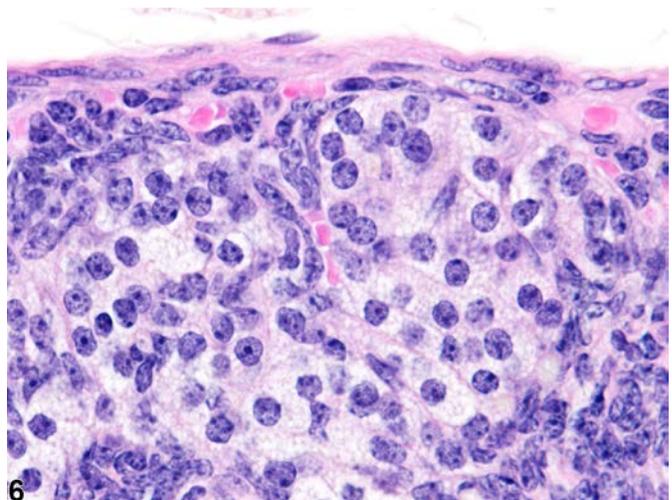
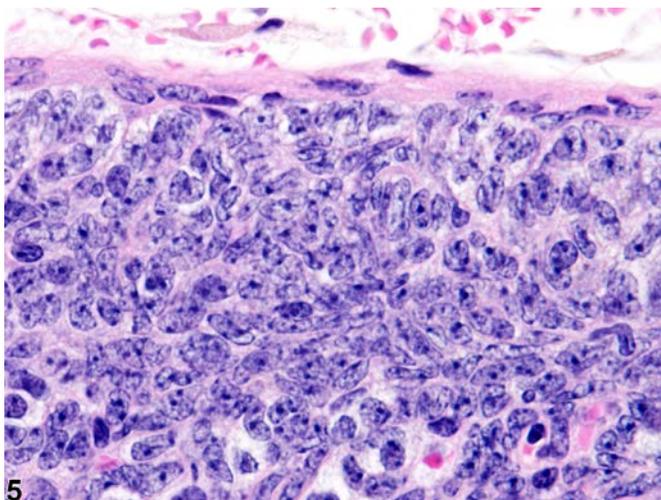
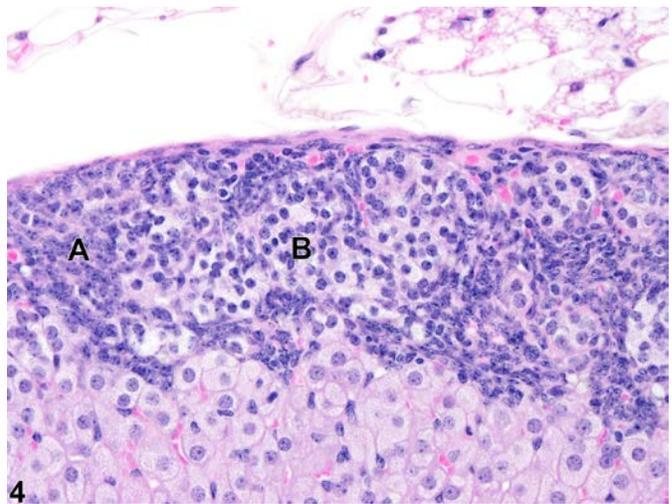
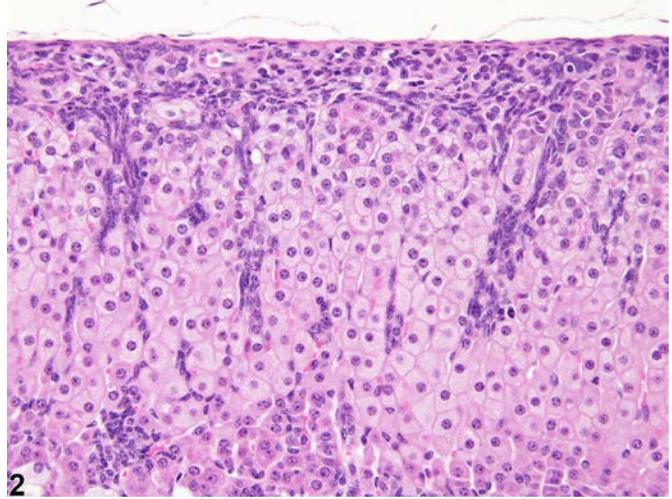
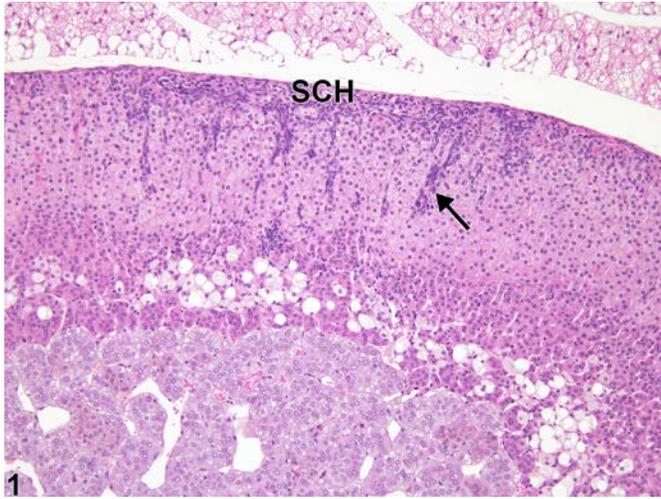
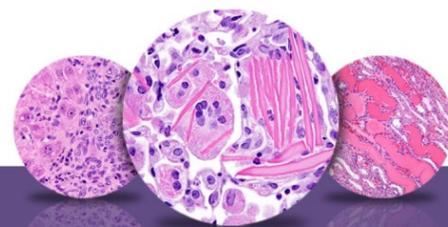


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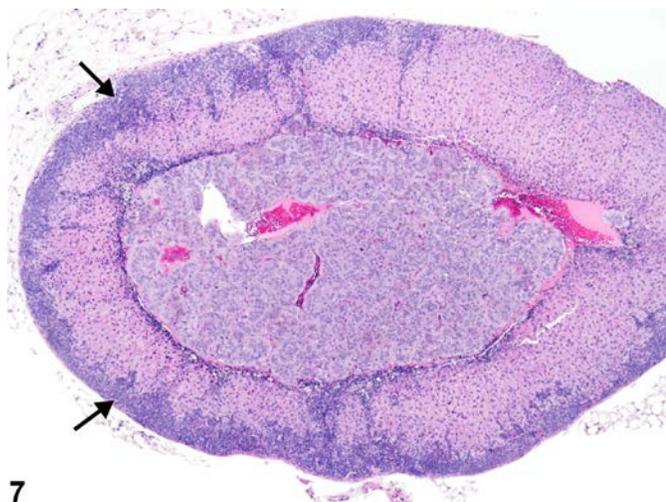
Adrenal Gland, Cortex – Hyperplasia, Subcapsular



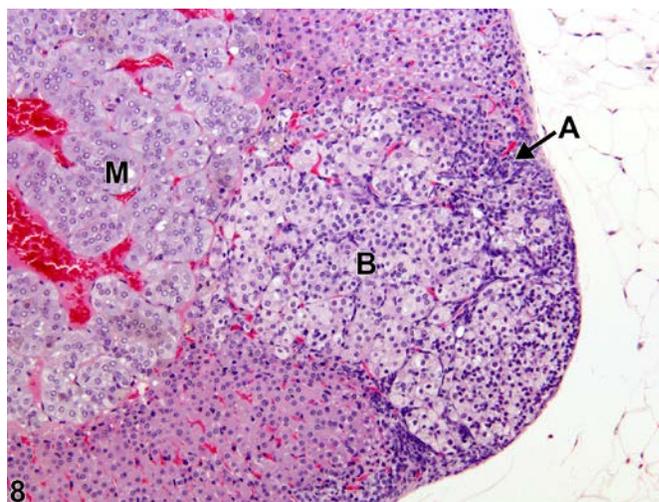


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Figure Legend: **Figure 1** Adrenal gland, Cortex - Hyperplasia, Subcapsular in a female B6C3F1/N mouse from a subchronic study. Early-stage subcapsular cell hyperplasia (SCH) is characterized by subcapsular foci of small, basophilic cells that extend into the zona fasciculata (arrow). **Figure 2** Adrenal gland, Cortex - Hyperplasia, Subcapsular in a female B6C3F1/N mouse from a subchronic study (higher magnification of Figure 1). Early-stage subcapsular hyperplasia is composed primarily of smaller, more basophilic, fusiform, type A cells that extend into the zona fasciculata. **Figure 3** Adrenal gland, Cortex - Hyperplasia, Subcapsular in a female B6C3F1/N mouse from a chronic study. Multiple foci of basophilic hyperplastic cells (arrows) are present in the subcapsular region. **Figure 4** Adrenal gland, Cortex - Hyperplasia, Subcapsular in a female B6C3F1/N mouse from a chronic study (higher magnification of Figure 3). The subcapsular hyperplasia is characterized by proliferation of smaller, fusiform, basophilic type A (A) cells with nests of larger, paler, polygonal type B cells (B). **Figure 5** Adrenal gland, Cortex - Hyperplasia, Subcapsular in a female B6C3F1/N mouse from a chronic study (higher magnification of Figure 3). Smaller, fusiform, basophilic type A cells are crowded together in a focus of subcapsular hyperplasia. **Figure 6** Adrenal gland, Cortex - Hyperplasia, Subcapsular in a female B6C3F1 mouse from a chronic study (higher magnification of Figure 3). Nests of larger, paler, polygonal type B cells are present in a focus of subcapsular hyperplasia. **Figure 7** Adrenal gland, Cortex - Hyperplasia, Subcapsular in a female B6C3F1/N mouse from a chronic study. Extensive subcapsular hyperplasia (arrows) forms a thick, almost circumferential band around the adrenal gland. **Figure 8** Adrenal gland, Cortex - Hyperplasia, Subcapsular in a male B6C3F1/N mouse from a chronic



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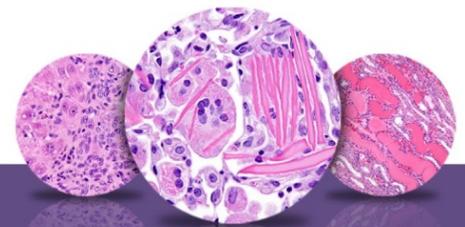
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study. A large subcapsular hyperplastic lesion is composed predominantly of polygonal type B cells (B) with fewer fusiform type A cells (A). M = medulla.

Comment: Adrenal cortical subcapsular hyperplasia (Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, Figure 7, and Figure 8) has been seen only in mice, and not in rats. It is a very common spontaneous finding in older mice of most strains, so incidences and severity generally increase with age. The lesion is also much more common and typically more extensive in female than in male mice. Subcapsular cell proliferation (hyperplasia and neoplasia) can be induced in certain mouse strains by gonadectomy.

This change is characterized by increased numbers of adrenal cortical subcapsular cells, generally considered to be the multipotential stem/progenitor cells that replenish senescent cells in the inner cortical zones. Under appropriate hormonal stimulation, the subcapsular cells can transdifferentiate into sex-steroid-producing cells resembling stromal gonadal cells. Two morphologically different types of subcapsular cells may be present in subcapsular hyperplastic lesions: elongated, spindle or fusiform type A cells (Figure 5) with elliptical nuclei and scanty basophilic cytoplasm, and larger, round or polygonal type B cells (Figure 6) with more abundant, pale to clear cytoplasm and round nuclei. Early hyperplastic lesions (Figure 1 and Figure 2) consist of small, often linear foci composed primarily of the spindle-like type A cells. The cell clusters are located initially in the zona glomerulosa adjacent to the capsule (Figure 1 and Figure 2), but as the cell aggregates enlarge due to proliferation, they extend centripetally as narrow to broad wedges intercalated between the underlying zona fasciculata cell cords and in linear sheets parallel to the adrenal capsule (Figure 1, Figure 2, and Figure 3). As the hyperplastic lesions enlarge, type B cells appear, and with further progression the ratio of polygonal type B cells to spindle type A cells usually increases (Figure 3 and Figure 4). Multiple foci in a given adrenal gland may coalesce to form an almost continuous band of hyperplastic cells subjacent to the capsule (Figure 7). Very large foci (Figure 8) are often composed almost entirely of polygonal type B cells, with few elongated type A cells, and can exhibit some degree of compression and expansion.

Focal subcapsular hyperplasia is considered a proliferative lesion in a morphologic continuum that can progress to adenoma and, rarely, to carcinoma. Subcapsular adenomas are also composed of variable mixtures of well-differentiated “spindle” and “polygonal” cells, so differentiating large focal hyperplasias



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from smaller adenomas can be challenging. Compared with hyperplastic foci, adenomas are larger, are more discretely nodular, clearly compress the adrenal parenchyma, and may even bulge prominently above the capsular surface due to pronounced expansile proliferation.

Recommendation: Adrenal cortical subcapsular hyperplasia should be diagnosed and assigned a severity grade.

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