Lung – Crystals

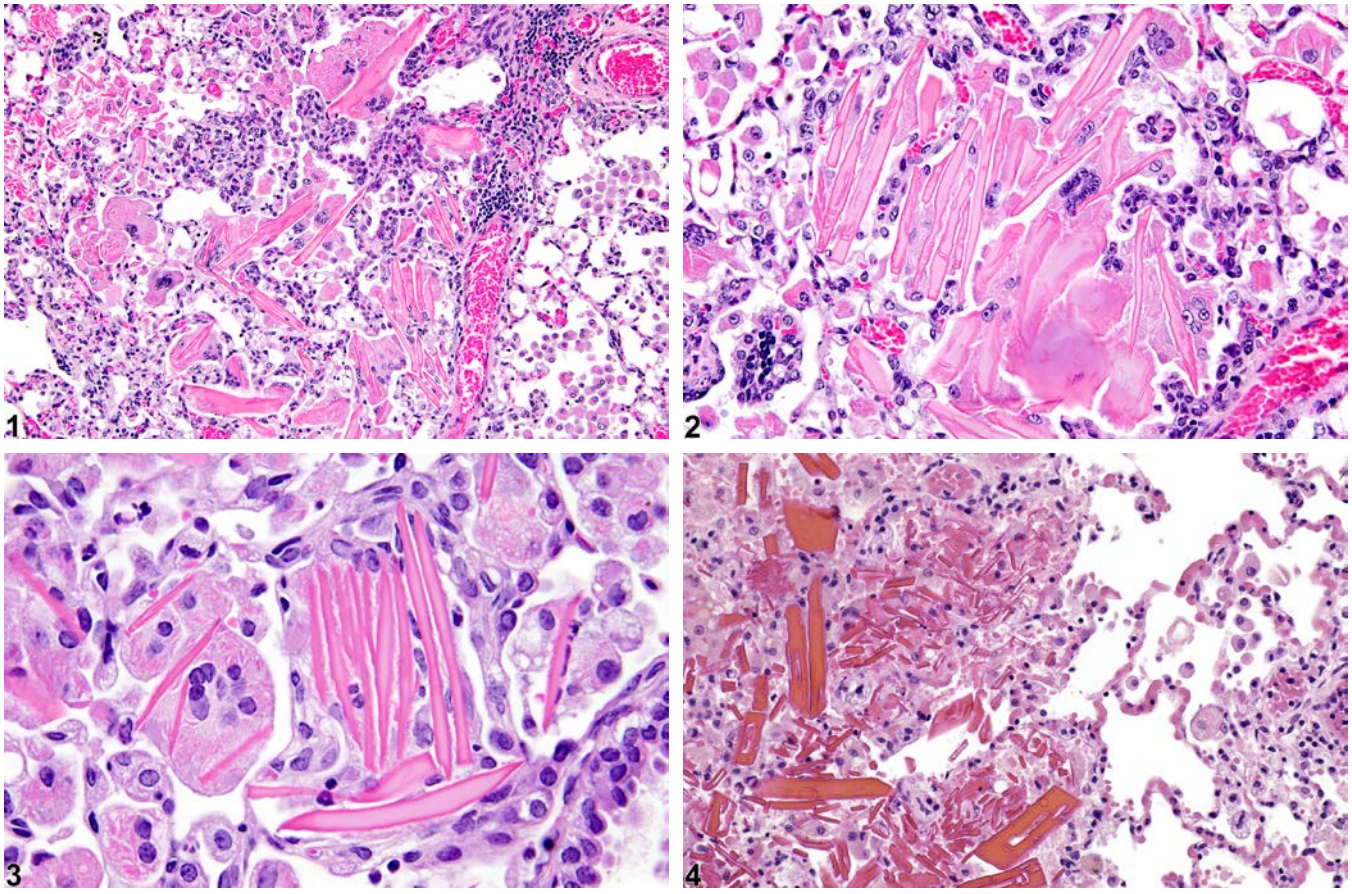
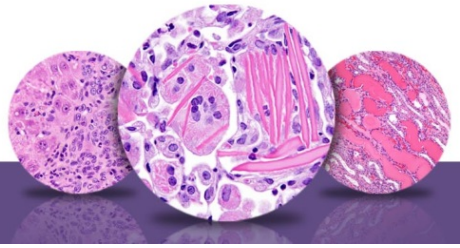


Figure Legend: **Figure 1** Lung - Crystals in a male B6C3F1/N mouse from a chronic study. Acicular, eosinophilic crystals and associated granulomatous inflammation are present in the alveoli. **Figure 2** Lung - Crystals in a male B6C3F1/N mouse from a chronic study. The eosinophilic crystals are largely extracellular. **Figure 3** Lung - Crystals in a male B6C3F1/N mouse from a chronic study. The larger crystals are extracellular, and the smaller crystals are within macrophages or multinucleated giant cells. **Figure 4** Lung - Crystals in a male F344/N rat from a chronic study. These deeply eosinophilic, variably shaped crystals are associated with hemorrhage.

Comment: In NTP studies, intrapulmonary crystals are most often seen in mice in inhalation studies with particulates (Figure 1, Figure 2, and Figure 3) or associated with neoplasms. The crystals are frequently seen with agents that cause significant alveolar proteinosis. The crystals are eosinophilic and acicular, or spindle shaped. Some larger crystals may be elongated rectangles, or “brick shaped.” They



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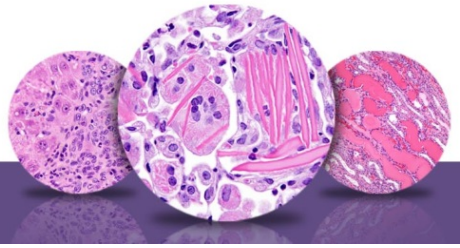
are usually present in the alveolar spaces and are associated with histiocytic infiltrates or, in more severe cases, granulomatous inflammation. The crystals are often surrounded by large macrophages, which may be multinucleated, and some smaller crystals may be within the cytoplasm of the macrophages and multinucleated giant cells. Some macrophages may contain numerous small crystals (Figure 3). Typically, variable numbers of other inflammatory cells (lymphocytes, plasma cells, neutrophils) are present in the interstitium or in the alveolar spaces.

Hemoglobin crystals are occasionally seen in areas of hemorrhage (Figure 4), often associated with inflammation. This type of crystal is most commonly seen in rats because rat hemoglobin crystallizes more readily than does hemoglobin in other species. Only structurally abnormal hemoglobin crystallizes in vivo in other species. Hemoglobin crystals are typically rectangular and, as opposed to the eosinophilic crystals of eosinophilic crystalline pneumonia, form in the extracellular space, though smaller hemoglobin crystals may be phagocytosed by alveolar macrophages. They typically resemble red blood cells in color and are usually spatially associated with extravasated erythrocytes.

Eosinophilic crystalline pneumonia is an idiopathic disease that occurs in mice. It can be a sporadic background lesion, with the severity varying from mild and subclinical to severe, in which case it may cause death. It may be seen in some genetically engineered mice (e.g., $p47^{phox-/-}$ mice) or mouse strains developed from naturally occurring mutations (e.g., $Ptpn6^{me}$ motheaten mice). Susceptible strains include C57BL/6 and 129Sv mice. The pathogenesis of eosinophilic crystalline pneumonia is unclear. It has been associated with eosinophilic inflammation in susceptible strains, such as that caused by parasitic and fungal infections, though the main cell type associated with the crystals is the alveolar macrophage. The crystals are immunoreactive to anti-Ym1 protein antibodies (a.k.a. T-lymphocyte-derived eosinophil chemotactic factor). Eosinophilic crystalline pneumonia is histologically similar to the crystals (and inflammation) associated with inhalation of particulates but does not occur with any relation to treatment and would also be seen in control mice.

Other types of crystals have been identified in rodent lungs. Subchronic exposure of rats to clofazimine, an antileprotic drug, leads to deposition of reddish orange crystals in many tissues, including lung. Chronic dietary administration of kojic acid in F344 rats produced pulmonary microgranulomas containing crystals. *Cryptococcus neoformans* infection in C57BL/6 mice generated rod-like crystalline



structures found associated with yeast cells or free in host cell cytoplasm. Though these crystals appear morphologically similar to those seen in murine eosinophilic crystalline pneumonia, these crystals are presumed to be the product of interaction of a host protein and a capsular cryptococcal polysaccharide.

Recommendation: Crystals both intracellular and free within airspaces should be diagnosed as Lung - Crystals and graded whenever present. A thorough description of the crystals, including size, shape, color, location, and whether they are intra- or extracellular (and the cell types in which they are found), should be included in the pathology narrative. Accompanying inflammation should be diagnosed and graded separately. If they are part of an inflammatory lesion associated with a neoplasm, they need not be diagnosed but should be described in the pathology narrative. If, in the opinion of the pathologist, the crystals are part of murine eosinophilic crystalline pneumonia, this should also be noted in the pathology narrative.

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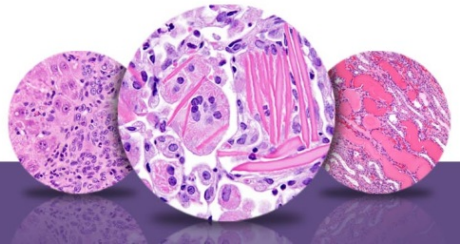

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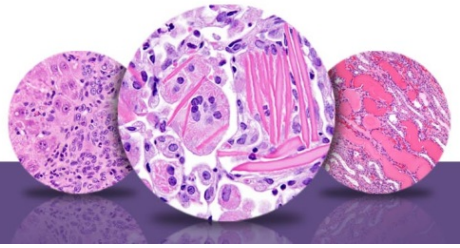

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