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**The pathology of *Francisella tularensis* SchuS4 in *Cynomolgus* macaques**

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*F. tularensis* is considered a biothreat agent due to the high degree of infectivity and virulence of specific strains. As such, well-characterized animal models are needed to test vaccines and therapeutic agents.

**Aim:** Our aim was to characterize the pathophysiology of aerosolized SchuS4 in *Cynomolgus macaques*.

**Methods:** As part of a study to determine the lethal dose 50% for aerosolized *F. tularensis*, *Cynomolgus macaques* were exposed to varying aerosol doses of SchuS4, and tissues were collected for pathologic evaluation at the time of death.

**Results:** Doses of SchuS4 ranged from 1 to greater than 10<sup>6</sup> CFUs. Animals died or were euthanized due to severe clinical disease over the course of several weeks, with a time to death that depended upon inoculum dose. Lesions were detected primarily in the nasal cavity, lungs, pleura/thoracic cavity, spleen, liver, lymph nodes and bone marrow, and less commonly in other tissues. Lesions in most organs consisted of macrophage and neutrophilic infiltrates, with prominent necrosis of parenchyma and infiltrating cells, vasculitis, fibrin exudation and hemorrhage. Higher doses were associated with miliary lung lesions and minimal lesions outside of the respiratory tract/thoracic cavity. Mid-range doses were associated with multifocal, nodular to cavitating lung lesions and development of necrotizing inflammation in the spleen and peripheral lymph nodes. Low doses were associated with sparse, nodular to cavitating lung lesions, prominent necrotizing inflammation in the spleen and peripheral lymph nodes, and sporadic necrotizing inflammation in other tissues (brain, kidneys, eyes).

**Conclusions:** The pathology of aerosolized *F. tularensis* in *Cynomolgus macaques* is similar to humans. The widespread distribution of lesions in the animals exposed to lower inoculum doses is interpreted to be a consequence of their prolonged post-exposure survival.

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