MedImmune
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CASE REPORT

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History

- Sexually mature Chinese origin female *Macaca fascicularis*
- 26-week toxicology study with an experimental therapeutic antibody, an anti-CD40L, high-dose group
- Abnormal clinical pathology changes on SD 141
- PE on SD 149 – splenomegaly, confirmed by ultrasound
- Scheduled necropsy on SD 192
  - Splenomegaly, nodular and abnormal in appearance
  - Several abrasions on the skin of the face
  - Adhesion in the abdominal cavity

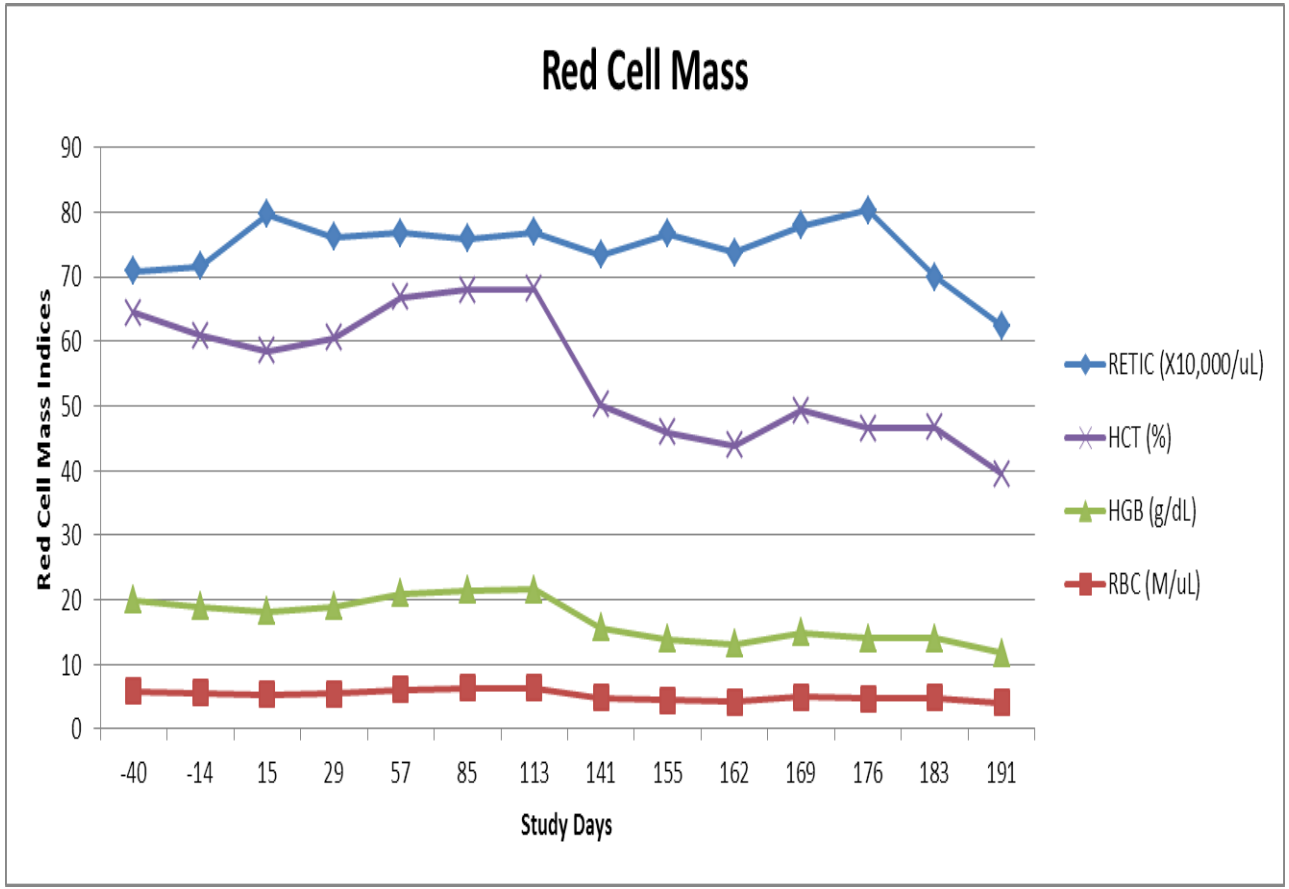
Clinical Pathology

- Decreased erythrocyte mass and leukocyte counts and increased ALP on Day 141

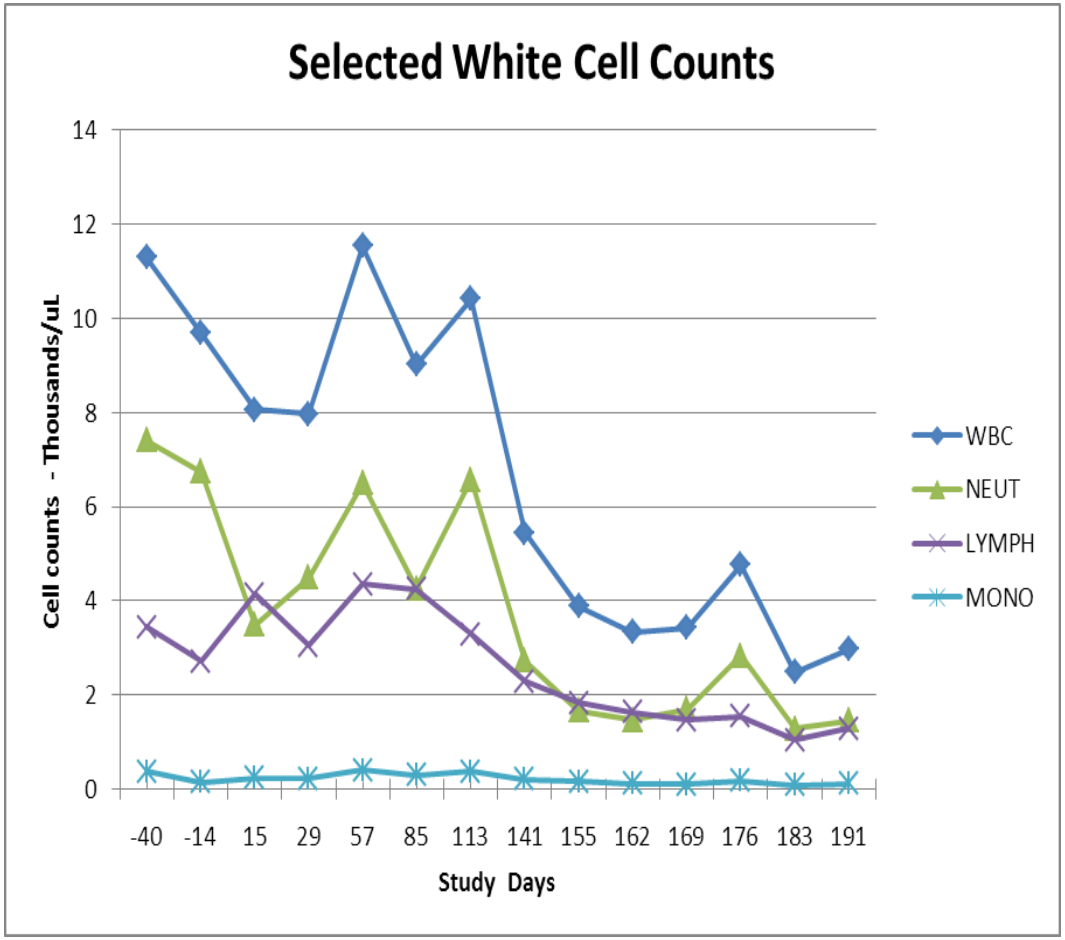
- Additional clinical pathology evaluations on Days 155, 162, 176, and 183

- Splenic impression smears and bone marrow smears were made and examined at terminal necropsy on Day 192

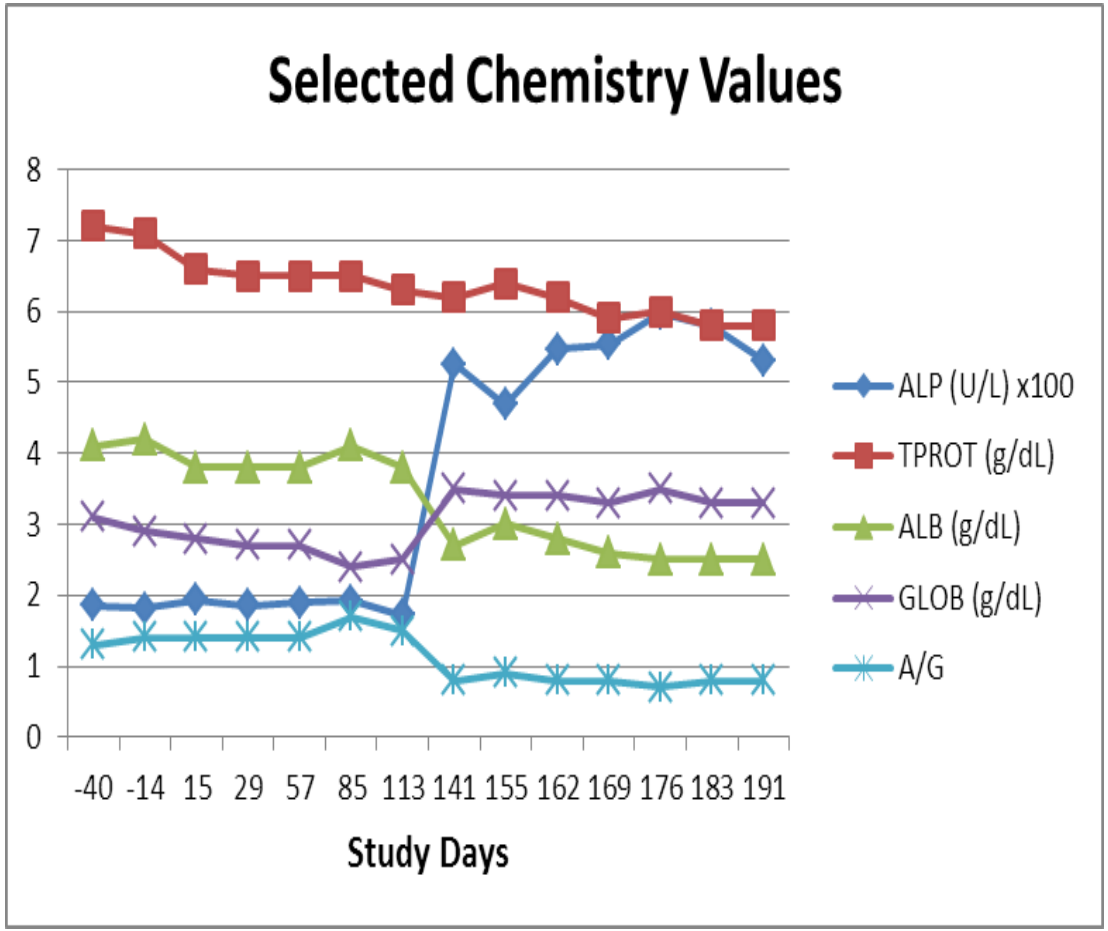
Clinical Pathology



Clinical Pathology



Clinical Pathology



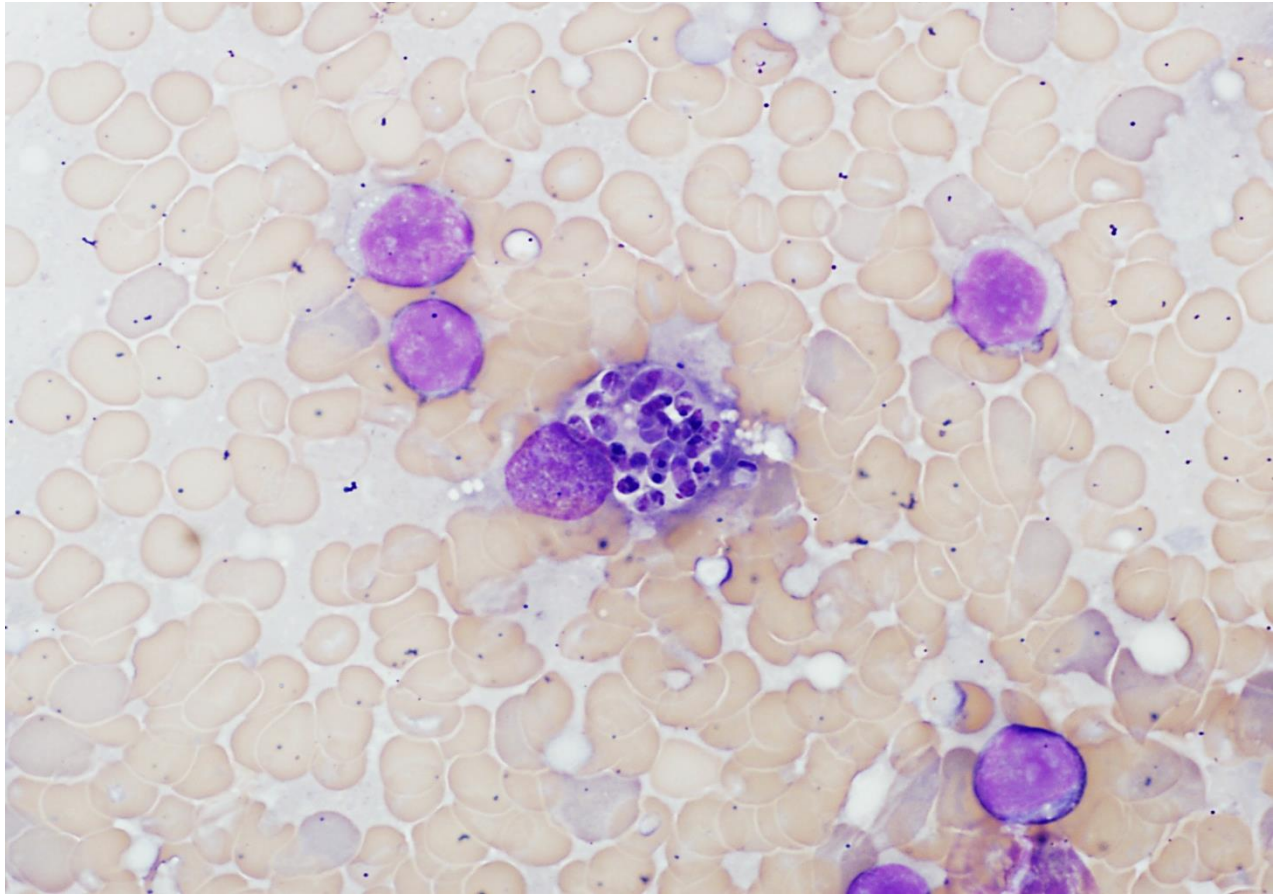
Cytology - Spleen

- Increased numbers of macrophages, which contained oval to round organisms with eccentric to centrally located nuclei

- Increased numbers of neutrophils, eosinophils, and basophils, erythrophagocytosis

- Nucleated erythroid precursors indicative of extramedullary hematopoiesis

Images - Cytology



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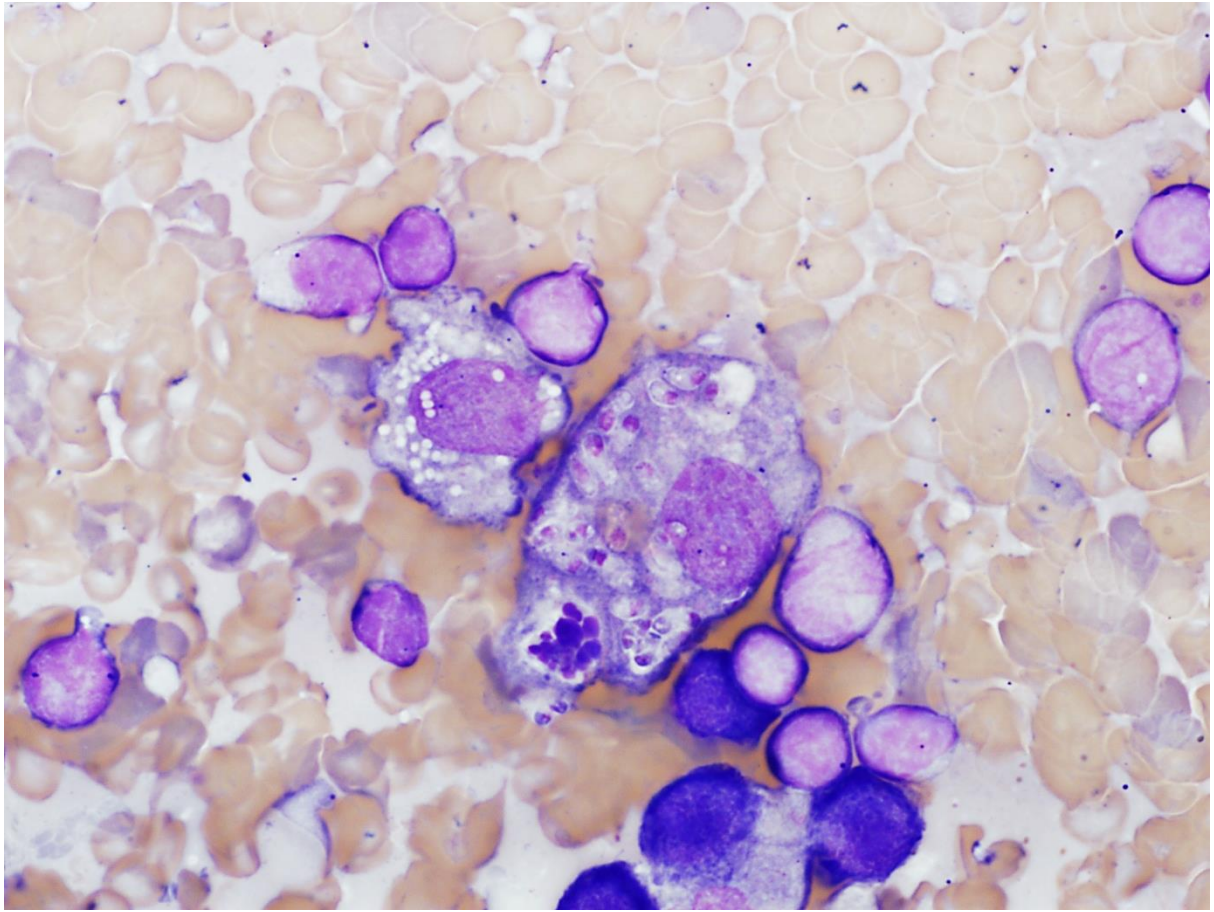

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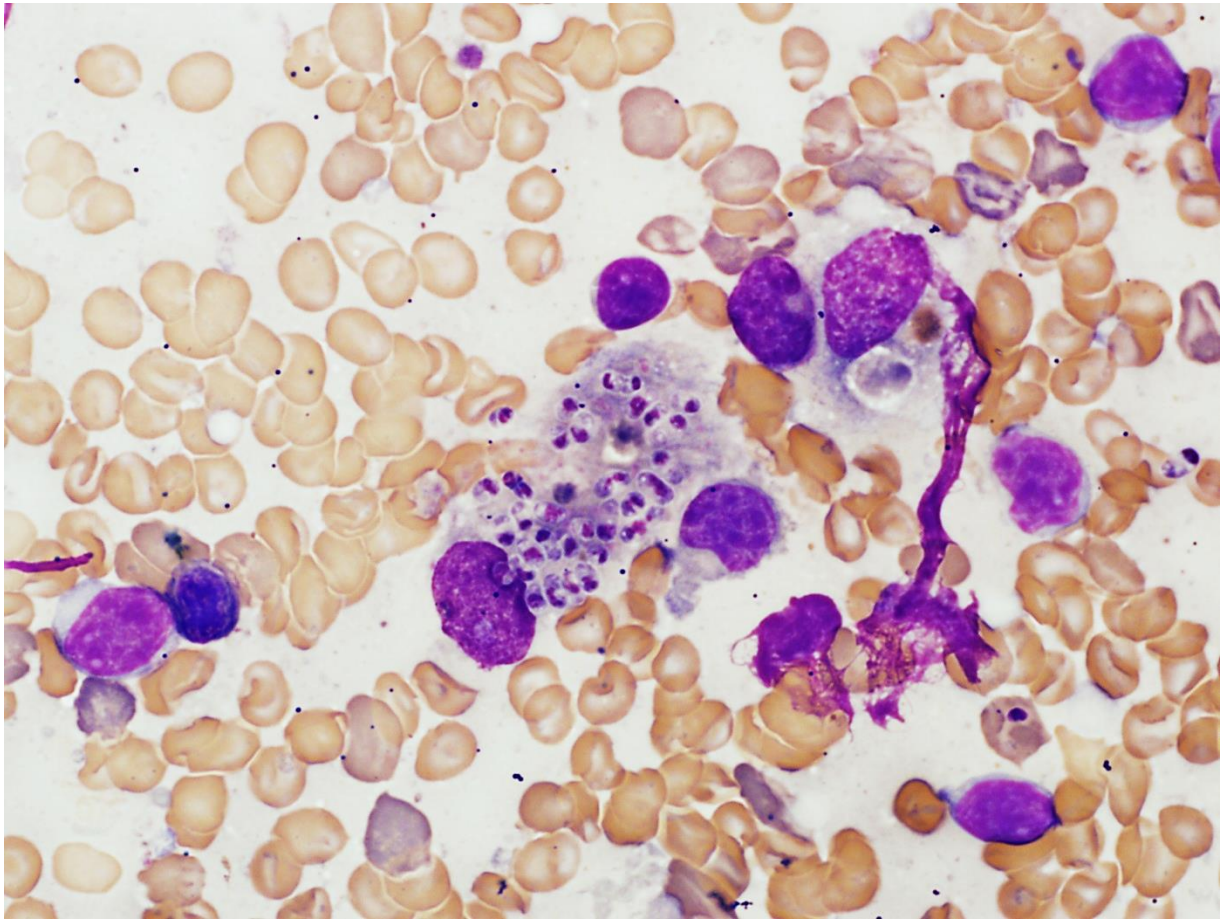


Necropsy

- Skin/Subcutis: Abrasion with several scabs on the lower jaw.
- Spleen: Marked enlargement and nodular. Multifocal tan firm foci on the splenic capsule. On cut surface it was a homogeneous deep red with a meaty consistency.
- Peritoneal cavity: Adhesion between body wall and viscera.

Necropsy - spleen

Spleen weight Vs. Control means

		Female Controls
• ***Absolute (g)***	***61.0***	***3.06***
• ***% Brain Weight***	***93.5***	***4.81***
• ***% Body Weight***	***2.10***	***0.74***

Histopathology

Tongue: This section of tongue has thinning of the mucosa in one focal area with an erosion and infiltration of small numbers of neutrophils. Beneath this lesion and extending into the skeletal muscle is an intense cellular infiltrate of macrophages with small numbers of lymphocytes. The macrophages are sometimes vacuolated and contain abundant eosinophilic cytoplasm which upon higher magnification is seen to contain numerous structures 2 to 4 μ in size consisting of basophilic dots surrounded by a clear circle or oval zone. The basophilic dots may be single or two close together.

Morphologic Diagnoses

– **Tongue**: 1) Erosion, focal, minimal, mucosa

2) Inflammation, acute, focal, minimal, mucosa

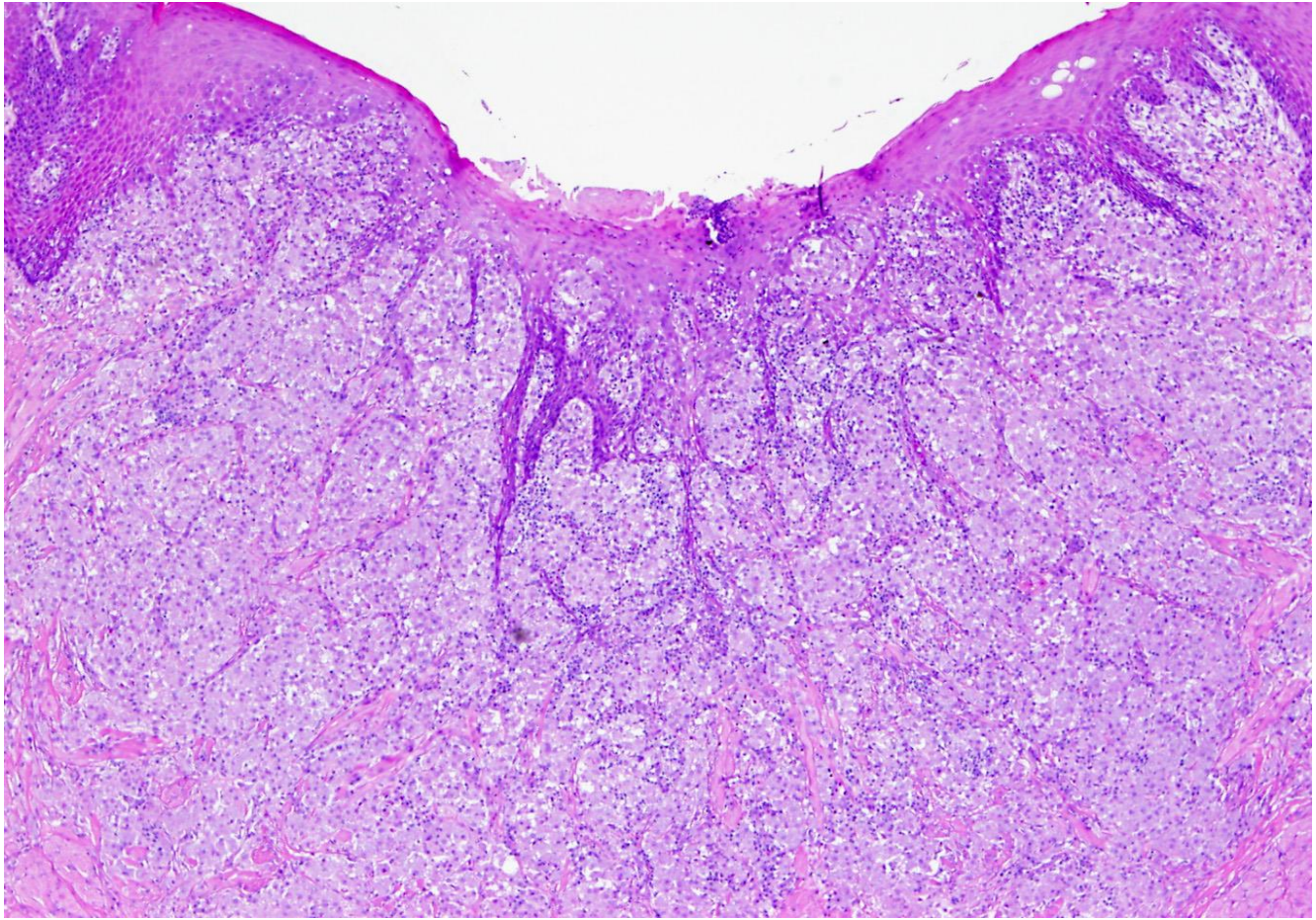
3) Inflammation, chronic, granulomatous, multifocal, severe, submucosa, with intracytoplasmic organisms

Etiology: *Talaromyces (Penicllium) marneffei*

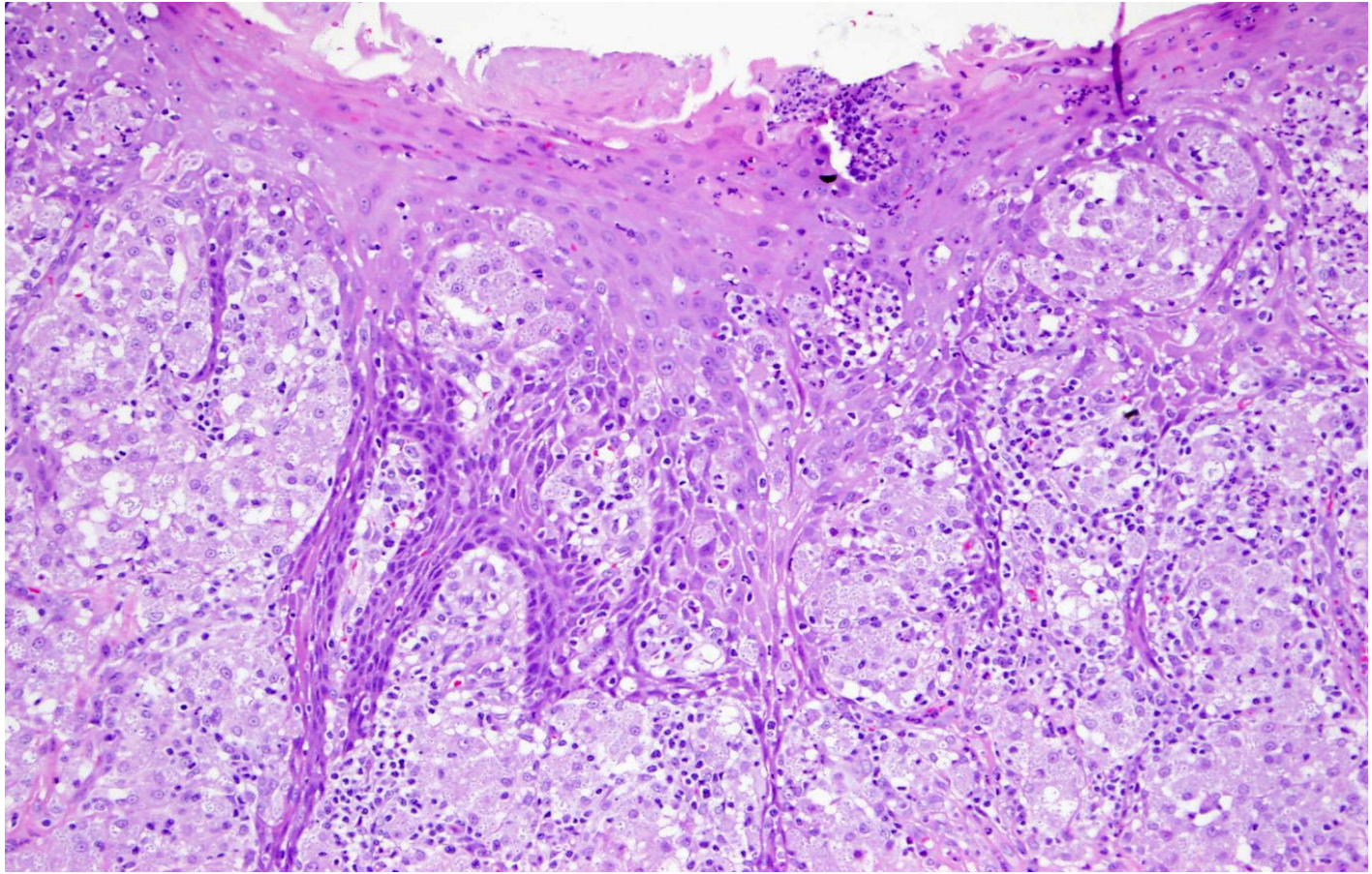
Identification confirmed by the Fungal Reference Unit, Mycotic Diseases Branch, National Center for Emerging and Zoonotic Infectious Diseases, CDC, Atlanta, GA, USA.

Images – Tongue

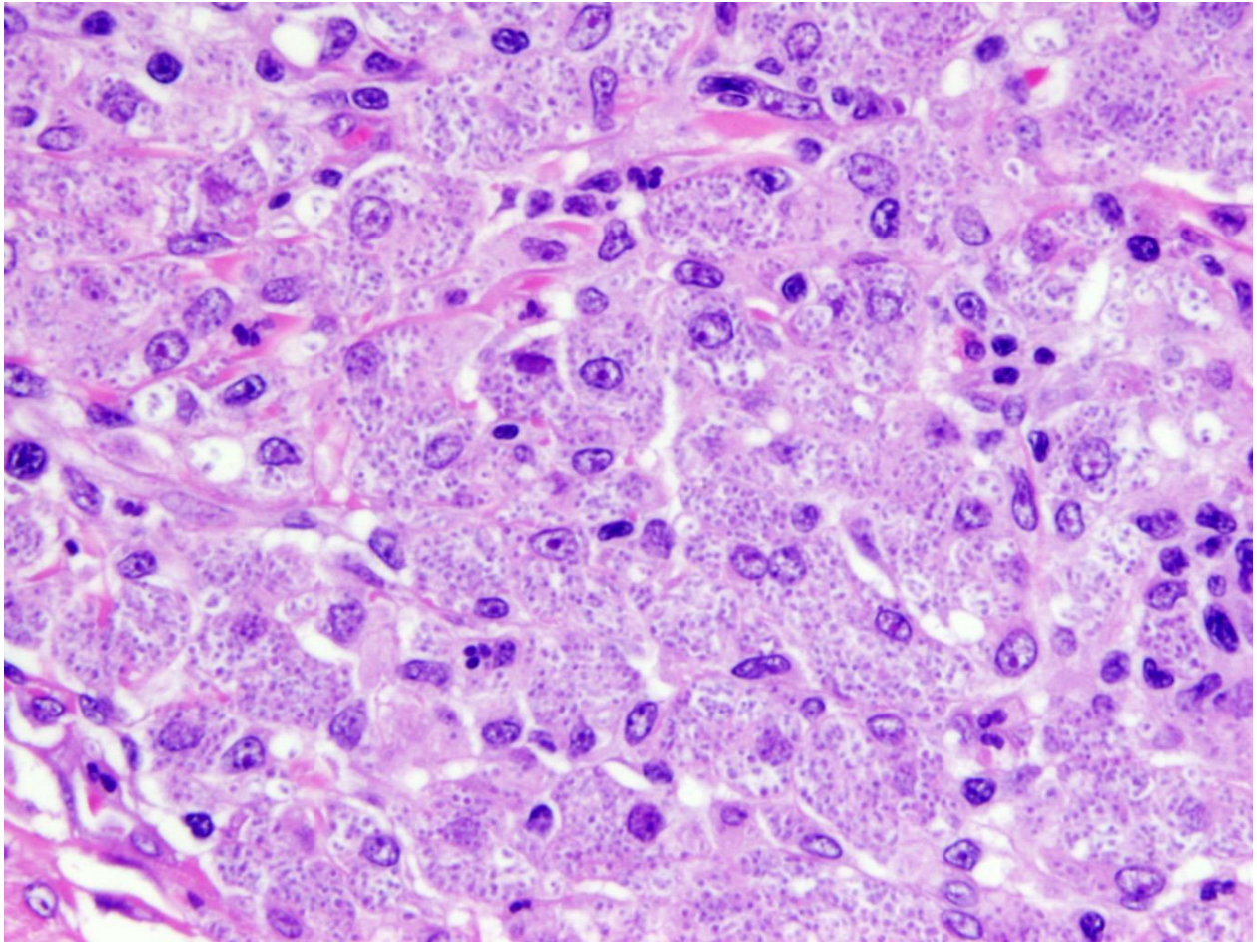
Images - Tongue



Images – Tongue



Images – Tongue



Systemic Pathology

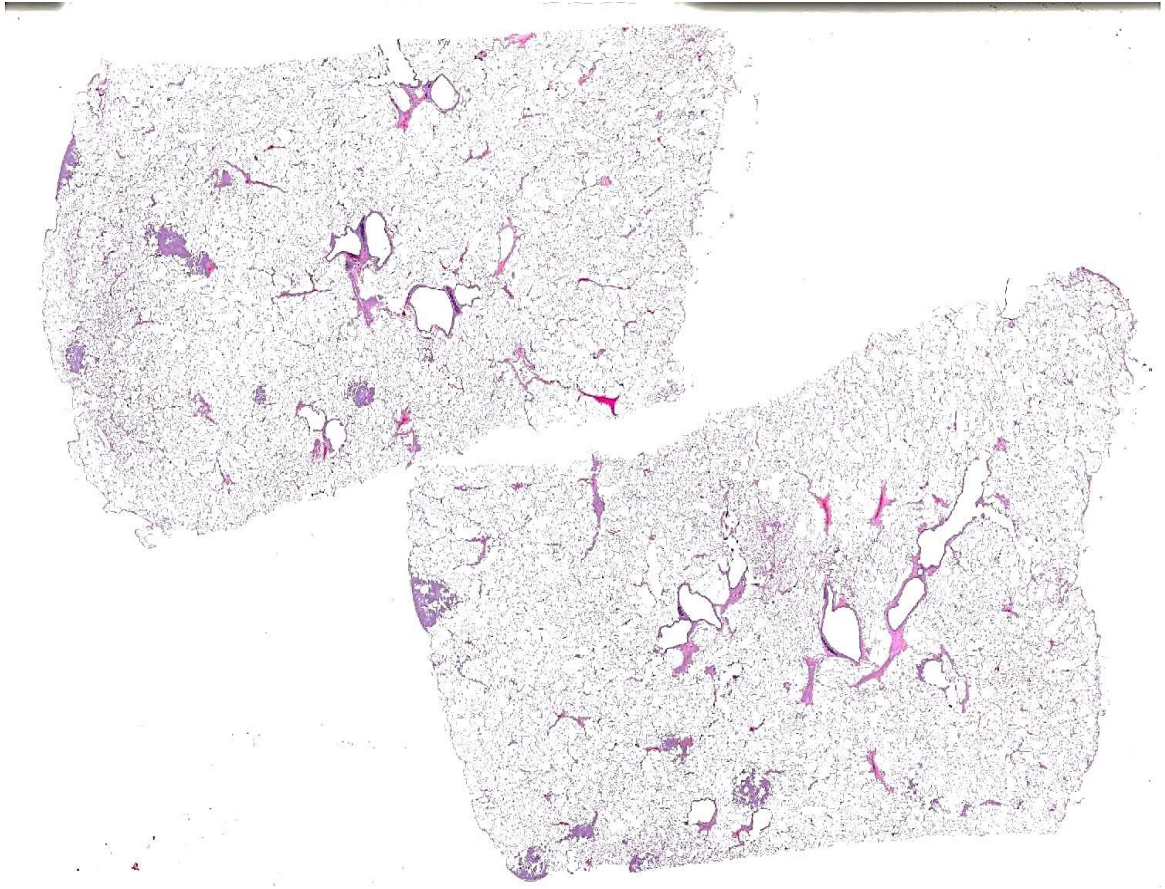
All but one section of skin, all sections of lymph nodes, spleen, liver, lung, femoral bone marrow, and many other tissues had slight to severe infiltrates of mononuclear cells, predominately macrophages, containing large numbers of yeast organisms in their cytoplasm. Fungal cultures (blood, kidney, spleen, liver, lung and urine collected at necropsy), and PCR evaluation of frozen tissues (liver and spleen, conducted at CDC) confirmed the presence of *Talaromyces (Penicillium) marneffei* which was further identified by DNA sequencing. *Talaromyces* sp. has been identified as part of normal flora on the skin of Cebus monkeys, and the ulcers on the skin of the face may have been the portal of entry. However, the organism spread systemically and was widely distributed throughout the body. Talaromycosis has not previously been reported in macaques.

Systemic Pathology

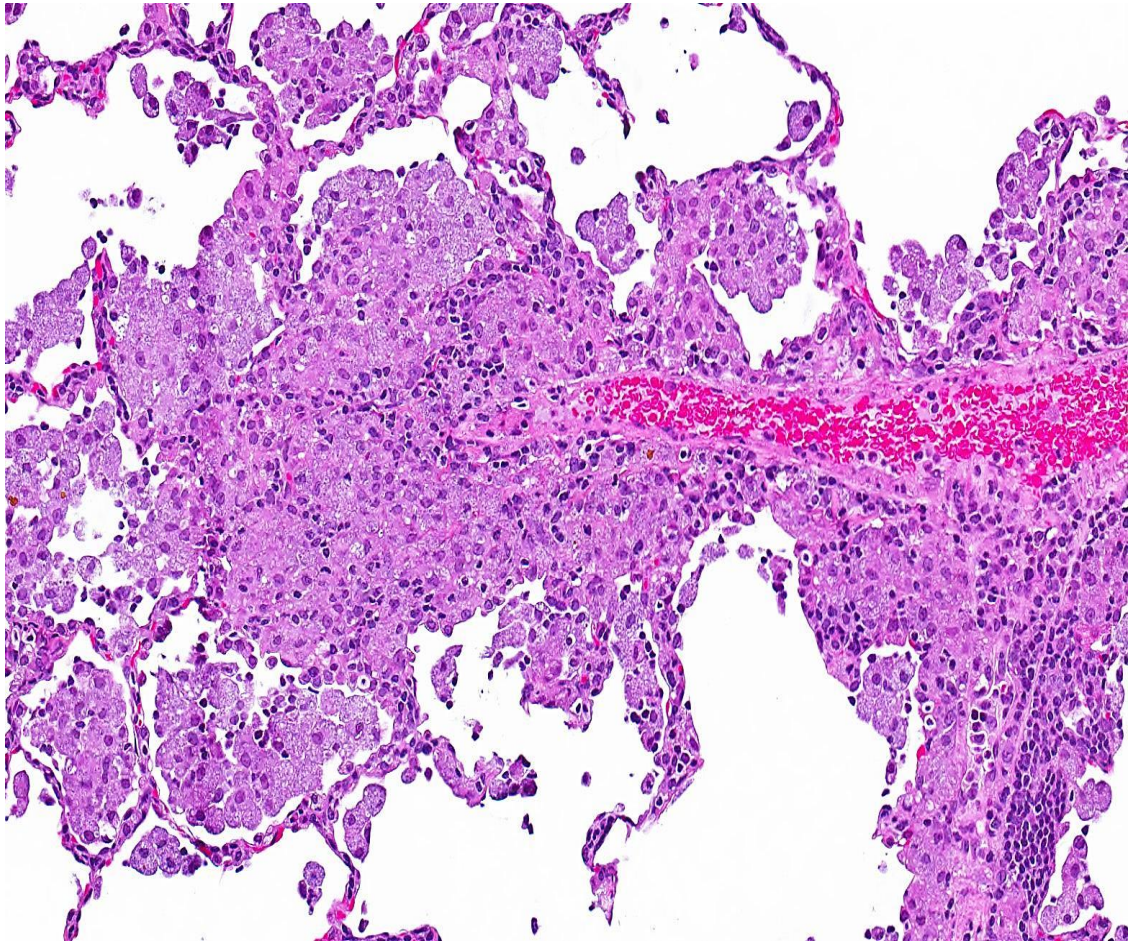
Granulomatous inflammation with organisms was found in the following tissues:

- Bone marrow
- Brain
- Cervix
- Liver
- Lung
- Mandibular, mesenteric, and mediastinal lymph nodes
- Omentum
- Rectum
- Skin/Subcutis
- Spleen
- Thymus
- Tongue
- Vagina

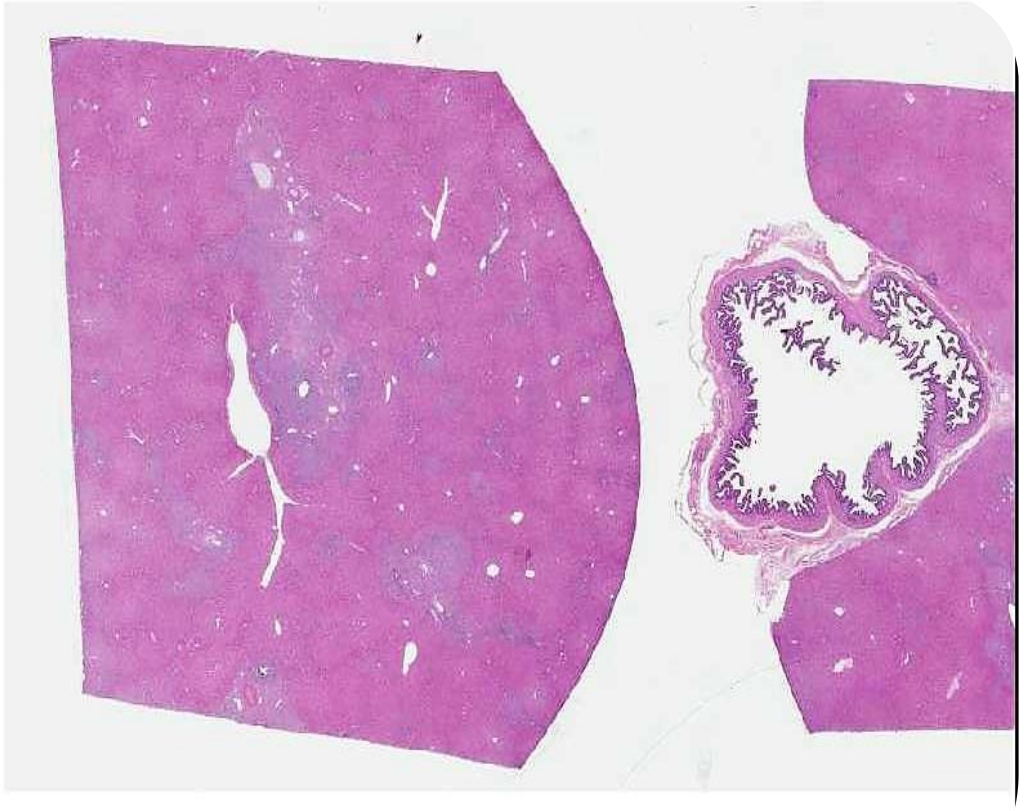
Histopathology - Lung



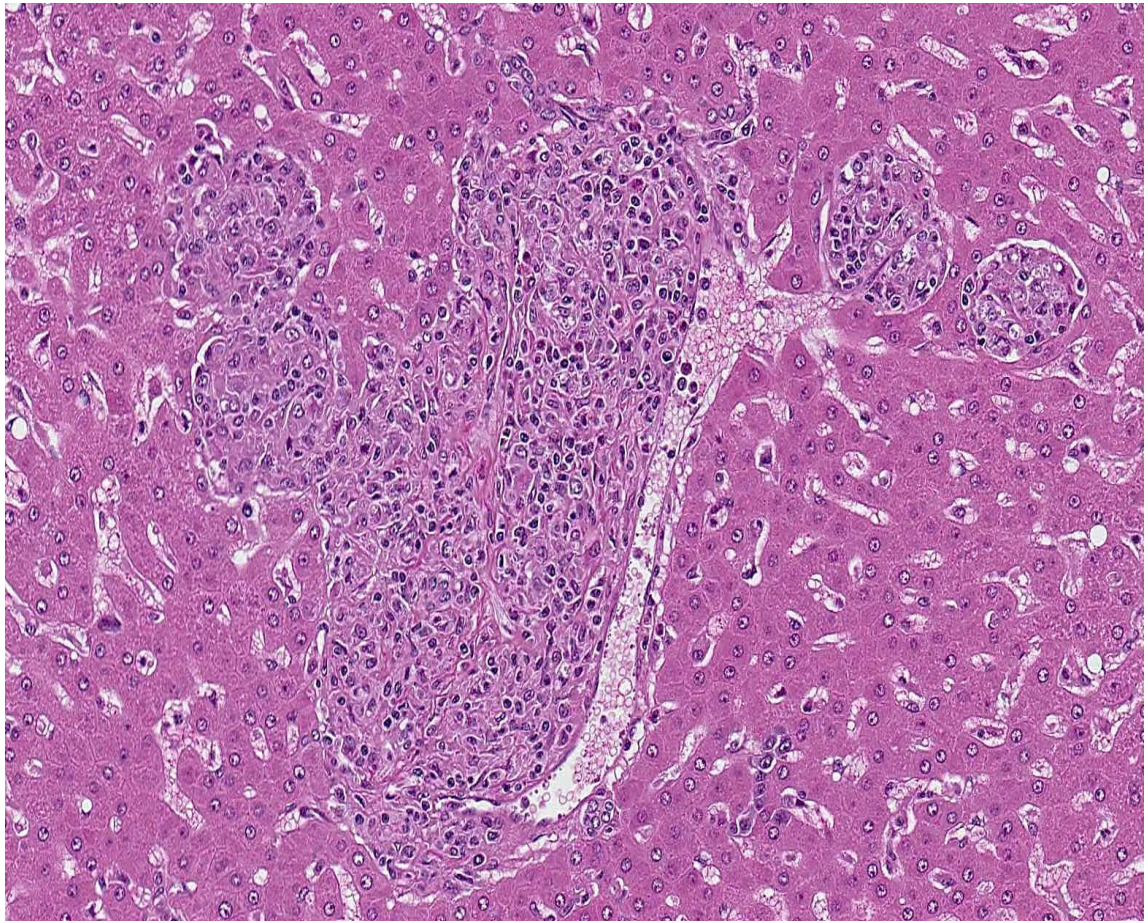
Histopathology - Lung



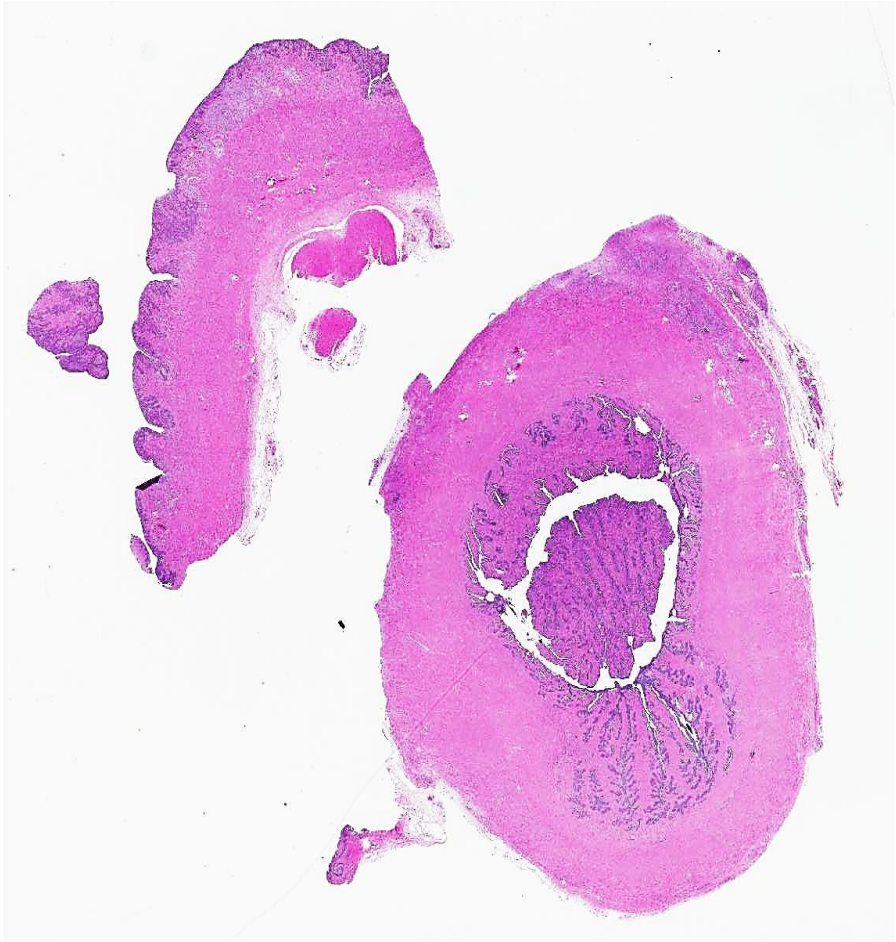
Histopathology – Liver



Histopathology - Liver



Histopathology – Vagina and Cervix



Histopathology - Skin

Talaromyces marneffei History

Talaromyces marneffei was first isolated from the hepatic lesions of a bamboo rat (*Rhizomys sinensis*) that had been maintained in captivity for experimental infections at the Pasteur Institute of Indochina, Dalat, South Vietnam, in 1956.

This bamboo rat died spontaneously from the reticuloendothelial mycosis. The fungus was named *Penicillium marneffei*, in honor of Hubert Marneffe, Director of the Pasteur Institute of Indochina. It was reclassified in 2015 by gene sequencing into the genus *Talaromyces*.

Talaromyces marneffei History

Talaromyces marneffei is an emerging pathogenic fungus that can cause a fatal systemic mycosis in patients infected with human immunodeficiency virus (HIV). *T. marneffei* infection is endemic in tropical Asia, especially Thailand, northeastern India, China, Hong Kong, Vietnam, and Taiwan.

The importance of *T. marneffei* as a human disease was not recognized until the HIV pandemic arrived in Asia and prevalences of infection increased in local populations as well as in visitors from areas where the infection is not endemic. The disease was, after tuberculosis and cryptococcosis, the third most common opportunistic infection in patients with AIDS in northern Thailand.

Talaromyces marneffei History

In addition to AIDS patients, it is also found in those with cell-mediated immunodeficiencies involving the IL-12/INF-γ signaling pathway, those receiving anti-CD20 therapeutics, chronic administration of T-lymphocyte depleting drugs, or kinase inhibitors. It has been rarely reported among hematologic cancer patients.

The organism can secrete laccase and Mp1p as factors that reduce the innate immune response and may play a role in the persistence of the yeast in macrophages.

References

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