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## KEY FACTS

### ETIOLOGY/PATHOGENESIS

- *Mycobacterium tuberculosis* is most common bacterial cause worldwide
- *Histoplasma* is common fungal cause
- CMV is most common adrenotropic agent in HIV patients
- Adrenal cortical infection and necrosis may also contribute to electrolyte imbalance and circulatory collapse in emerging viral infections including Ebola hemorrhagic fever and Middle East respiratory syndrome

### CLINICAL ISSUES

- Infectious adrenalitis with adrenal insufficiency are underdiagnosed causes of morbidity and death
- Fatal adrenal crisis can be 1st sign of adrenal insufficiency
- Variable recovery after resolution of infections

### MICROSCOPIC

- Pathology varies with specific organism, immune status, and other host factors

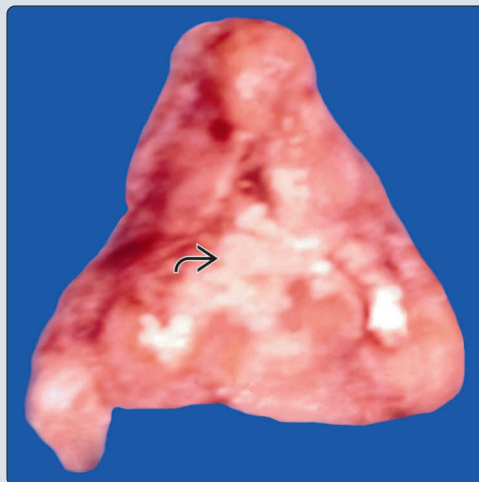
- **Tuberculosis:** Chronic inflammation, giant cells, and caseation; granulomas can be less developed than with TB in other sites; possibly due to high local steroid concentration
- **Other bacteria:** Neutrophilic abscesses, organisms sometimes seen, sometimes with blood vessel invasion
- **Viral infections:** Lesions vary from focal necrosis to diffuse destruction of gland
  - **CMV:** Large cells with amphophilic intranuclear inclusions and granular basophilic cytoplasmic inclusions, mixed inflammation, variable necrosis
  - **Herpes and Varicella-Zoster:** Eosinophilic intranuclear inclusions, variable necrosis, minimal inflammation

### TOP DIFFERENTIAL DIAGNOSES

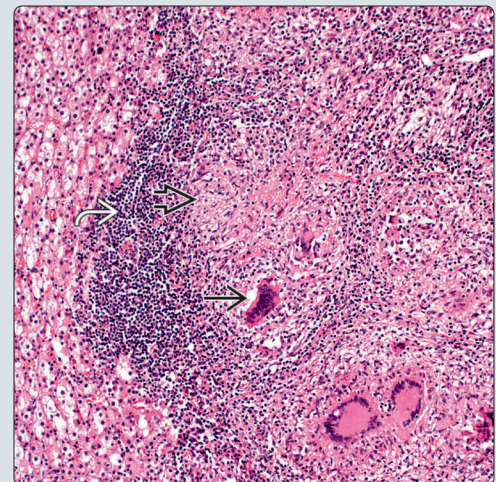
- **Autoimmune adrenalitis:** Lymphoplasmacytic infiltrate; no granulomas, no neutrophils
- **Lymphoma/leukemia:** Monomorphic, monotypic infiltrate, often cytologically distinctive

**Tuberculosis Gross Cut Surface**

(Left) Adrenal gland affected by tuberculosis shows extensive areas of caseous geographic necrosis involving both the cortex and the medulla. (Right) In adrenal tuberculosis, the granulomas are often less developed than in tuberculosis at other sites. Lymphocytes, giant cells, and foci of caseous material are present. Adrenocortical tissue is at left.

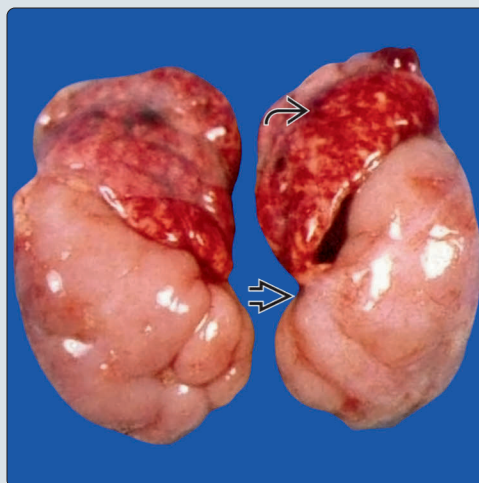


**Granulomas in Tuberculosis**

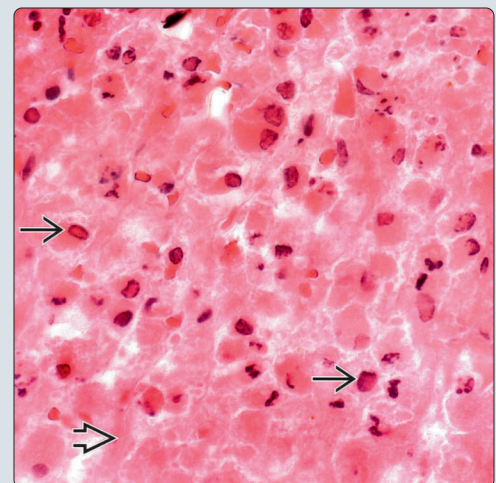


**Gross of Herpes Simplex Infection**

(Left) Gross photo of transplacental herpes simplex infection shows multiple pinpoint areas of necrosis and calcification within the adrenal cortices. The kidneys appear externally normal. (Right) In disseminated Herpes simplex, adrenal cortical cells show eosinophilic intranuclear inclusions and necrosis.



**Herpes Simplex Inclusions**



## ETIOLOGY/PATHOGENESIS

### Infectious Agents

- Many organisms infect adrenal glands, including bacteria, viruses, fungi, and parasites
- Infectious agent, histological manifestations, and severity of damage depend on tropism, immune status, and other host factors
  - Bacteria
    - *Mycobacterium tuberculosis* (TB) prevalent in developing countries
    - Others include *Pseudomonas*, *Treponema pallidum*, *Listeria*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus*
  - Fungi
    - *Histoplasma* is most common fungus infecting adrenal
    - Others include *Cryptococcus*, *Coccidioides*, *Paracoccidioides*, *Blastomyces*, and *Candida* spp.
  - Viruses
    - CMV is most common adrenotropic infectious agent in AIDS patients
    - Other viral infections: Herpesvirus group, Varicella-Zoster, HIV, coxsackie B, echovirus, Epstein-Barr virus, adenovirus
      - Adrenal cortical infection and necrosis may also contribute to electrolyte imbalance and circulatory collapse in Ebola hemorrhagic fever, Middle East respiratory syndrome, and other emerging viral infections
  - Parasites: Uncommon in developed countries, regional variations worldwide
    - Organisms include *Echinococcus* spp. (~ 7% of adrenal cysts), *Leishmania* spp., *Microspora* spp., *Trypanosoma cruzi*
- Waterhouse-Friderichsen syndrome is secondary adrenal manifestation of systemic bacterial infection
  - Usually occurs in children < 2 years old, occasional occult cases in adults with septicemia
  - *Neisseria meningitidis* is most common causative organism
  - Others include *Streptococcus pneumoniae*, group B *Streptococcus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*
  - Mechanism(s) still unclear; may involve stress-induced increase in ACTH, increased adrenal blood flow, cytokine activation, bacterial toxins, adrenal vasospasm, disseminated intravascular coagulation

## CLINICAL ISSUES

### Presentation

- Adrenalitis usually secondary to systemic infection but can be isolated finding; usually bilateral
  - TB adrenalitis seen in up to 6% of patients with active TB, *Histoplasma* adrenalitis in 30-50% of patients with disseminated *H. capsulatum*
  - Adrenalitis in HIV/Aids: Direct adrenal infection by HIV plus multiple potential opportunistic agents
    - CMV adrenalitis in ~ 50% of AIDS patients, sometimes without apparent other organ involvement
  - HSV adrenalitis associated with congenital/neonatal disseminated HSV

- Infection usually acquired during passage through birth canal, ~ 1/500-1/1500 births, ~ 20% of infections disseminated
- Occasional cases with transplacental infection

- Iatrogenic or endogenous hypercortisolism increases susceptibility and masks adrenal insufficiency
  - Stimulation of hypothalamic-pituitary-adrenal axis by stress of systemic infection
  - "Pseudo-Cushing" caused by antiretroviral agents in some patients
  - Possible direct effects of CMV on steroidogenesis

### Prognosis

- Uncontrolled or undetected infection can proceed to acute or chronic adrenal insufficiency, underdiagnosed causes of morbidity and death
  - Occur in 5-8% of patients with HIV infection, up to 47% with advanced AIDS
  - TB is most common infectious cause worldwide; histoplasmosis is most common fungal cause
  - Fatal adrenal crisis (acute adrenal insufficiency) can be 1st sign of adrenal insufficiency
- Variable recovery after resolution of infections
- Waterhouse-Friderichsen syndrome fatal in majority of cases

## IMAGING

### General Features

- In active TB infection: Enlarged glands with hypoattenuating necrotic areas ± calcifications in CT or x-ray; MRI may show marginal enhancement with persistent hypointensity of central areas
- Atrophy in advanced cases

## MACROSCOPIC

### General Features

- **Adrenal TB:** Glands up to 2-3x normal size; fibrocaseous tissue involving cortex and medulla is most prominent feature
- **Histoplasma:** Gland enlargement, caseation variably present
- **Systemic infections** with *Pseudomonas* spp. and *Listeria* spp.: Sharply punched-out necrotic areas
- **CMV, herpes, coxsackie B, and echovirus:** Punched-out or confluent areas of necrosis and hemorrhage
- **Waterhouse-Friderichsen syndrome:** Extensive hemorrhagic necrosis, usually bilateral

## MICROSCOPIC

### Histologic Features

- **Bacterial and fungal infections**
  - **Tuberculosis:** Chronic inflammation, giant cells, and caseation
    - Granulomas can be less developed than with TB in other sites; possibly due to high local steroid concentration
    - Subcapsular granulation tissue and calcifications in older lesions; medullary destruction
  - **Histoplasmosis and other fungi:** Epithelioid histiocytes, granulomas, and caseation variably present

- Fungal emboli in small vessels with some fungi
- Microscopic abscesses in disseminated candidiasis
- **Other bacteria:** Neutrophilic abscesses, organisms sometimes seen, sometimes with blood vessel invasion
- **Congenital syphilis:** Capsular and cortical fibrosis
- **Viral infections:** Lesions vary from focal necrosis to diffuse destruction of gland
  - **CMV**
    - Enlarged ("megalic") cells
    - Amorphophilic intranuclear inclusions with clear halo (Cowdry type A inclusions) plus granular basophilic cytoplasmic inclusions
    - Variable necrosis, mixed inflammation
  - **Herpesvirus and Varicella-Zoster**
    - Smudged eosinophilic intranuclear inclusion without halo (Cowdry type B inclusions) in early or primary infections
    - Large intranuclear inclusion with halo (Cowdry type A) may be found in older lesions
    - Multinucleated giant cells, nuclear molding
    - Variable necrosis, minimal inflammation
- **Waterhouse-Friderichsen syndrome:** Extensive hemorrhagic necrosis
  - Hemorrhage begins in zona reticularis and extends toward capsule and medulla; zona glomerulosa may be partly spared
  - Small fibrin thrombi suggesting diffuse intravascular coagulation variably present in sinusoids,
  - Healing adrenals may show stippled calcification and fibrosis

5. Rai B et al: Transient acute adrenal insufficiency associated with adenovirus serotype 40 infection. *BMJ Case Rep.* 2014, 2014
6. Upadhyay J et al: Tuberculosis of the adrenal gland: a case report and review of the literature of infections of the adrenal gland. *Int J Endocrinol.* 2014:876037, 2014
7. Tormos LM et al: The significance of adrenal hemorrhage: undiagnosed Waterhouse-Friderichsen syndrome, a case series. *J Forensic Sci.* 58(4):1071-4, 2013
8. Centers for Disease Control and Prevention (CDC): trends in tuberculosis—United States, 2010. *MMWR Morb Mortal Wkly Rep.* 60(11):333-7, 2011
9. Trevisan M et al: Human cytomegalovirus productively infects adrenocortical cells and induces an early cortisol response. *J Cell Physiol.* 221(3):629-41, 2009
10. Burrill J et al: Tuberculosis: a radiologic review. *Radiographics.* 27(5):1255-73, 2007
11. Guo YK et al: Addison's disease due to adrenal tuberculosis: contrast-enhanced CT features and clinical duration correlation. *Eur J Radiol.* 62(1):126-31, 2007
12. Ma ES et al: Tuberculous Addison's disease: morphological and quantitative evaluation with multidetector-row CT. *Eur J Radiol.* 62(3):352-8, 2007
13. Paolo WF Jr et al: Adrenal infections. *Int J Infect Dis.* 10(5):343-53, 2006
14. Wang YX et al: CT findings of adrenal glands in patients with tuberculous Addison's disease. *J Belge Radiol.* 81(5):226-8, 1998
15. Hayashi Y et al: Focal lymphocytic infiltration in the adrenal cortex of the elderly: immunohistological analysis of infiltrating lymphocytes. *Clin Exp Immunol.* 77(1):101-5, 1989

## ANCILLARY TESTS

### Histochemistry

- Special stains for suspected microorganisms
- Immunohistochemistry or in situ hybridization for optimal detection of virus-infected cells

## DIFFERENTIAL DIAGNOSIS

### Inflammatory Conditions

- **Autoimmune adrenalitis:** Lymphoplasmacytic infiltrate; no granulomas and no neutrophils
- **Focal lymphocytic infiltration in adrenal cortex of elderly:** Possibly preclinical manifestation of autoimmune adrenalitis; variable focal or patchy lymphocytic infiltrate, little or no cortical destruction
- **Sarcoidosis:** Noncaseating granulomas, often fused but discrete, other stigmata of systemic involvement

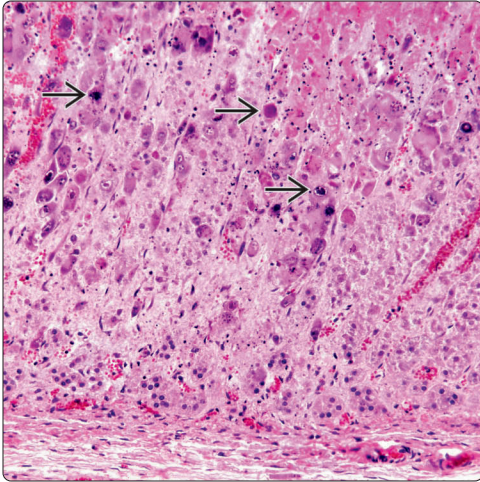
### Lymphoma/Leukemia

- Monomorphic, monotypic infiltrate, often cytologically distinctive

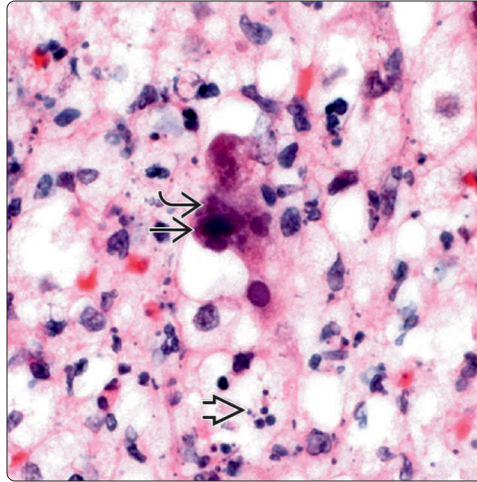
## SELECTED REFERENCES

1. Rushworth RL et al: Adrenal crises: perspectives and research directions. *Endocrine.* 55(2):336-345, 2017
2. El Sayed SM et al: Updates in diagnosis and management of Ebola hemorrhagic fever. *J Res Med Sci.* 21:84, 2016
3. Chan JF et al: Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. *Clin Microbiol Rev.* 28(2):465-522, 2015
4. Chrousos GP et al: Hypothalamic-pituitary-adrenal axis in HIV infection and disease. *Endocrinol Metab Clin North Am.* 43(3):791-806, 2014

CMV Inclusions

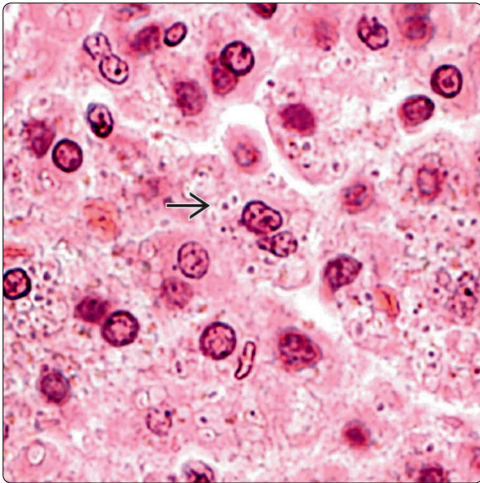


CMV Inclusion

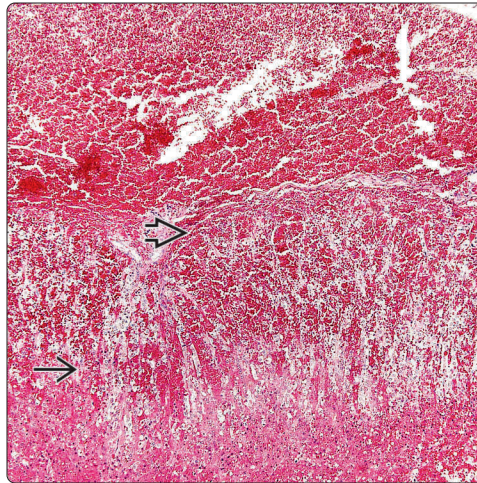


(Left) Disseminated CMV infection in the adrenal gland of a child with congenital immunodeficiency is shown. This specimen was obtained at autopsy and shows necrosis and many large cells that contain viral inclusions. (Right) In cytomegalovirus infection, the adrenal gland shows enlarged cells with amorphophilic nuclear inclusions with clear halo, cytoplasmic inclusions and variable necrosis.

Histoplasmosis

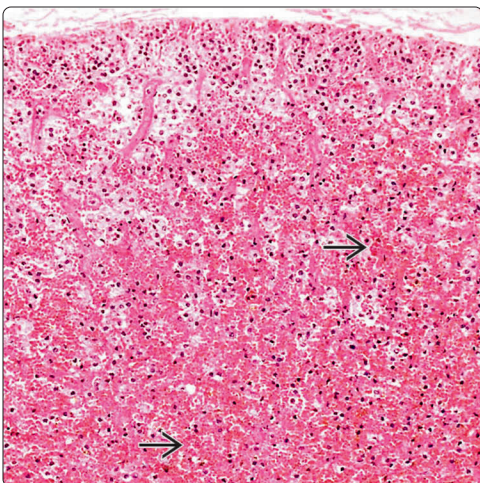


Waterhouse-Friderichsen Syndrome

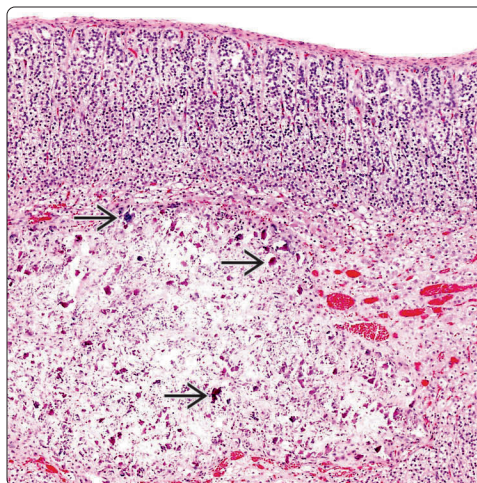


(Left) *Histoplasma capsulatum* is seen as tiny yeasts in the cytoplasm of macrophages admixed with cortical cells. Fixation artifact resembles an unstained capsule. (Right) An adrenal gland section in Waterhouse-Friderichsen syndrome shows cortical and subcapsular hemorrhage dissecting into the surrounding fibroadipose tissue.

Waterhouse-Friderichsen Syndrome



Posthemorrhagic Calcification



(Left) Higher magnification of the adrenal cortical hemorrhage is shown with associated necrosis of the adrenal cortical cells. (Right) Posthemorrhagic calcification is illustrated in this adrenal section. Note the stippled calcification. (From DP: Nonneoplastic Pediatrics.)