A Ratty Story

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History

- Adult intact male Zucker rat
- Part of a research protocol
- One of eight rats submitted for evaluation

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Gross Findings

- 8/8 rats underweight to emaciated
- 8/8 kyphosis
- 4/8 submandibular swelling
- 1/8 corneal/conjunctival keratinization
ACINAR ATROPHY

200X image of salivary gland

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Histopathology

- Marked chronic diffuse pyogranulomatous sialoadenitis with ductular squamous metaplasia, keratinization, and intralesional mixed bacteria
Additional Tests

Culture

- 1000 colonies Escherichia coli
- >200 colonies Gram negative nonfermentative rod (Acinetobacter or Stenotrophomonas)
- >100 colonies Gram positive anaerobic rod (Actinomyces-like)

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Etiology: Vitamin A Deficiency
Functions

- Vision
  - Rhodopsin

- Metabolism
  - Lipid
  - Bone

- Growth
  - Growth factor receptors
  - Tumor suppressor genes

- Resistance to infection
  - Intestinal barrier

- Anti-inflammatory
  - Neutrophil inhibition

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Sialoadenitis

- Early lesions
  - Glandular epithelial cell atrophy
  - Interstitial edema and fibroplasia
  - Decreased salivary secretion

- Decreased growth factor receptors
Sialoadenitis

- Neutrophilic and bacterial invasion of salivary ducts
- Decreased salivary flow
- Decreased neutrophilic inhibition
Later lesions
- Ductular squamous metaplasia and keratinization
  - Occlusion & rupture

Unclear pathogenesis
- Increased basal cell proliferation
- Decreased differentiation signals
- Alterations in biochemical milieu
Corneal/Conjunctival keratinization

Unclear pathogenesis
  › Increased basal cell proliferation
  › Decreased differentiation signals
  › Alterations in biochemical milieu
Additional Reported Lesions
Atrophy

- Thyroid gland
- Parathyroid glands
- Anterior pituitary
- Harderian glands
- Lacrimal glands
- Seminiferous tubules
- Prostate gland
- Seminal vesicles
- Coagulating gland
- Exocrine pancreas
- Brunner’s glands
- Sebaceous glands
Squamous metaplasia and keratinization

- Harderian glands
- Lacrimal glands
- Meibomian glands
- Upper respiratory epithelium
- Olfactory epithelium
- Trachea
- Bronchi
- Gastric epithelium*
- Pancreatic ducts

- Renal pelvis
- Ureter
- Urinary Bladder
- Seminiferous tubules
- Prostate
- Seminal vesicles
- Coagulating gland
- Oviduct
- Uterus
- Vagina

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Additional lesions by system

- **Respiratory**
  - Hyperplasia of the olfactory epithelium
  - Thickened alveolar BM
  - Impaired type II pneumocyte differentiation
  - Interstitial pneumonia

- **Cardiovascular**
  - Focal myofiber degeneration
Additional lesions by system

- **Alimentary**
  - Lingual ulcers*
  - Taste bud hyperkeratosis
  - Esophageal hyperkeratosis*
  - Decreased duodenal goblet cell numbers
  - Increased Lactobacillus and Escherichia coli

- **Hepatic**
  - Hepatocellular vacuolation
Additional lesions by system

- **Special Senses**
  - Retinal degeneration (photoreceptor)

- **Hematopoietic**
  - Splenic and thymic lymphoid depletion
  - Hyperkeratosis of Hassall’s corpuscles

- **Skeletal**
  - Kyphosis*
General considerations

- Emaciation*
  - Decreased intestinal absorptive capacity
  - Appetite suppression
  - Increased fatty acid oxidation
  - Lack of dietary palatability

- Secondary bacterial infection

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THANK YOU!

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Dee Stephenson
Sharon Schlosshen
Michelle Hill
David Durtschi
Any Questions?
General Pathology
Metabolism of Retinol

- Obtained from diet
  - Retinol esters and Carotenoids (β-Carotene)

- Transported to liver in chylomicrons
  - Bind hepatocellular apolipoprotein E receptor

- May be esterified for hepatic storage
Metabolism of Retinol

- Stored retinol released into circulation
  - Carried by hepatocellular Retinol Binding Protein

- Uptake by other cell types
  - Cell-specific Retinol Binding Proteins

- Hepatocellular Retinol Binding Protein released back into circulation
Metabolism of Retinol

- **Eye**
  - Oxidized to all-trans retinaldehyde
  - Isomerized to 11-cis retinaldehyde

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Metabolism of Retinol

- Other tissues
  - Oxidized to all-trans retinaldehyde
    - Alcohol dehydrogenases
    - Short-chain dehydrogenase/reductases
    - Cytochrome P450s
  - Further oxidized to all-trans retinoic acid
    - Aldehyde dehydrogenases
  - Some isomerized to 9-cis retinoic acid
Functions

- **Vision**
  - 11-cis retinal associates with 7 transmembrane rod protein → rhodopsin
  - Photon reaching rods isomerize 11-cis retinal to all-trans retinal
  - All-trans retinal dissociates
  - Conformational change in opsin
Functions

- Growth
  - All-trans retinoic acid binds to Retinoic Acid Receptors (RAR)
  - RAR forms heterodimer with Retinoic X Receptor (RXR)
  - RAR-RXR activates Retinoic Acid Response Elements (RARE) in promoter regions
    - Growth factor receptors
    - Tumor suppressor genes
Functions

- Resistance to Infection
  - Strengthens intestinal barrier
    - Promotes goblet cell differentiation
  - Promotes defensin production
  - Suppresses expression of TLRs 2 and 5
Functions

- Metabolism
  - 9-cis retinoic acid activates RXR
  - RXR forms heterodimers with PPARs and Vitamin D receptors
Functions

- RXR-PPARs
  - Fatty acid oxidation in adipose and muscle
  - Adipogenesis
- Lipoprotein metabolism

- RXR-Vitamin D receptors
  - Osteoclasia
  - Osteoblast secretory activity

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Functions

- Anti-inflammatory
  - Inhibits neutrophil superoxide production
  - Inhibits release of neutrophilic lysozomal enzymes
  - Decreases synthesis of LTB4


Asson-Batres MA et al. Vitamin A deficiency leads to increased cell proliferation in olfactory epithelium in mature rats.


Wolbach SB and Howe PR. Tissue changes following deprivation of fat-soluble vitamin A. The Journal of Experimental Medicine 42(6)753-777 (1925)