CASE 17

FANCONI-LIKE SYNDROME IN A SIV-INFECTED MACAQUES DURING HIGH-DOSE ANTIRETROVIRAL THERAPY

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History:

• 4.42-years-old, male Indian rhesus macaque (*Macaca mulatta*)

• Inoculated with SIVmac251 one year ago, and developed chronic viremia, low CD4 counts, chronic dehydration, and weight loss.
  • Treated with the antiretroviral drug PMPA (9-[2-(r)-(phosphonomethoxy) propyl] adenine or tenofovir (30 mg/kg of body weight) subcutaneously once daily for 2 months.
  • Humanely euthanized due to the poor prognosis.

• Hematology:
  • Lymphocytes: 24.1% (35.2-84.1%). All others were in the normal ranges.

• Biochemistry

• Urinalysis
  • Not available.
Major gross findings:

• Thin body condition with minimal body fat.

• Lungs failed to completely collapse with multifocal to coalescing, dark-red, meaty foci on the pleural surface and within the pulmonary parenchyma.

• Diffusely both kidneys were pale white to yellow.

• The spleen and all peripheral lymph nodes were 2-3x enlarged.
Pneumocystis pneumonia
Morphologic Diagnosis and Etiology:

• Kidney, nephropathy characterized by nuclear dysplasia, interstitial fibrosis, PCT eosinophilia, tubular proteinosis, tubular necrosis, interstitial nephritis, and cellular casts, consistent with Fanconi-like syndrome caused by PMPA (tenofovir) toxicity.

• Lung. Pneumocystis pneumonia (not submitted).
Comment:

- Due to its efficacy and safety, PMPA has been commonly used for treating both HIV and hepatitis B virus infections.

- Prolonged treatment of macaques with a high dose of PMPA (30 mg/kg of body weight subcutaneously once daily) can result in proximal renal tubular dysfunction.
  
  - A Fanconi-like syndrome characterized by glucosuria, aminoaciduria, hypophosphatemia, and bone pathology.

- Chronic administration of a low dose of PMPA (10 mg/kg subcutaneously once daily) has no any adverse health effects within 3 years of treatment.

- PMPA is a nucleotide reverse transcriptase inhibitor.

  - An analog of dAMP, PMPA inhibits the activity of HIV-1 or SIV reverse transcriptase by competing with natural substrate thymidine triphosphate and by causing DNA chain termination following its incorporation into viral DNA.
• The toxicity of PMPA is probably due to its renal clearance. PMPA and its related nucleotide analogs are excreted in unchanged form in urine through a combination of renal filtration and active tubular secretion.

• Due to more drug uptake from plasma than secretion into the tubular lumen, the drug accumulates in tubular epithelial cells and causes renal disorder by direct renal epithelial damage.

• The proximal tubule epithelial cell is the main target of PMPA toxicity due to its complement of cell membrane transporters that favor PMPA accumulation.

• Current evidence suggests that mitochondria are the target organelles of PMPA cytotoxicity by decreasing mitochondrial DNA replication through inhibition of mtDNA polymerase γ.
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References


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