Oxidative stress and inflammasome activation in human rhabdomyolysis-induced acute kidney injury (RIAKI)

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Background

- Rhabdomyolysis is a clinical syndrome characterised by rapid disintegration of skeletal muscle, releasing toxic intracellular contents (e.g. myoglobin and uric acid) into the peripheral circulation.

- Acute kidney injury (AKI) is the most severe systemic complication of rhabdomyolysis, with reported mortality rates as high as 59%.

- Recent experimental investigations using mouse models have identified the molecular pathways driving RIAKI pathogenesis – including tubular oxidative damage and cell death (necroptosis), inflammation and activation of the inflammasome pathway.

- In this study, we investigated, for the first time, the cellular and molecular pathways of RIAKI in humans.

Method

- 37 year old male.
- Muscle damage (serum creatinine kinase 40,900 U/L; ref range 46-171)
- Severe AKI (serum creatinine 1030 µmol/L; baseline 100 µmol/L).
- Streptococcus pyogenes (group A) cultured from two peripheral blood samples.
- A diagnostic renal biopsy reported tubular injury and 24% of glomeruli reported as sclerosed.
- The patient required three sessions of haemodialysis with recovery of kidney function to baseline one month post-discharge.

Case Report

- FIGURE 1 Tubular myoglobin casts and birefringent crystals in human RIAKI.
- FIGURE 2 Significantly elevated uric acid levels, tubular oxidative stress (4-HNE staining), regulated tubular necrosis/necroptosis (pMLKL staining) and inflammation (TNF-α staining) in RIAKI tissue compared to healthy control.
- FIGURE 3 Significantly increased accumulation of inflammatory immune cells - macrophages (CD68), dendritic cells (CD1c) and T cells (CD3) - in RIAKI tissue adjacent to sites of tubular injury.
- FIGURE 4 Significantly increased expression of inflammasome adaptor protein ASC and active caspase-1 within immune cell infiltrate in human RIAKI.

Results

- We provide first evidence in human RIAKI of molecular pathways previously described in animal studies associating myoglobin and uric acid deposition with tubular oxidative stress, necroptosis, tubulointerstitial inflammation, immune cell infiltration and inflammasome activation.

- Our findings are the first to translate these shared pathogenic drivers of murine RIAKI into the human system.

- These new insights into the cellular and molecular pathways of human RIAKI reveal novel targets for diagnostic and therapeutic intervention.

Conclusion

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