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## L-amino-acid oxidase from *Bothrops leucurus* venom induces nephrotoxicity via apoptosis and necrosis

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The pit viper *Bothrops leucurus* (White-tailed-jararaca) is a poisonous snake habituating area in the northeast of Brazil. The biological effects due envenomation have similar profile than those observed with other *Bothrops*, such as coagulant activity, hemorrhagic, fibrinolytic and acute renal failure (ARF). ARF is a common complication caused by *Bothrops* snakebite with relevant morbidity and mortality. Pathogenesis of ARF in snakebite envenomation may be related to hypo-volemia and hypo-perfusion secondary to cardiovascular disturbances, deposit of fibrin in the glomerular capillaries leading thrombotic micro-angiopathy and high venom concentration at the renal tissue, direct venom action on the tubular cells and oxidative stress. Recently, we observed that *Bothrops leucurus* venom induces nephrotoxicity in the isolated perfused kidney of rats associated with cytotoxicity against renal tubular epithelia cells. In this study, it was evaluated the direct nephrotoxicity of a main component of *B. leucurus* venom called L-aminoacid oxidase (LAAO-BI) by using tubular epithelial cell lines MDCK and HK-2. In these cells treated with LAAO-BI, 1.56–100 µg/mL for 12 h, there was a decrease in their viability in a concentration-dependent manner. We next evaluated if necrosis was implicated in the cellular viability decrease observed by analyzing lactate dehydrogenase (LDH) release. In MDCK cells LDH release was not observed after 12 h of LAAO-BI exposure while LAAO-BI induced an apparent membrane rupture in HK-2 cells at the highest concentrations studied when compared with untreated cells. Annexin V/PI staining was applied to detect apoptotic/necrotic cells after LAAO-BI treatment. In MDCK cells, LAAO-BI significantly increased the percentage of early apoptotic (Annexin-V+, PI-), necrotic (Annexin-V-, PI+) and secondary necrotic cells (Annexin-V+, PI+) when compared with control untreated cells. In HK-2 cells, in accordance with data obtained in the LDH-release assay, the Annexin-V-PI loading cell analysis demonstrated an increase in necrotic (PI+ cells) and secondary necrotic cells (Annexin-V+, PI+) in a concentration-dependent manner. MDCK and HK-2 apoptosis induction was accompanied with Ca<sup>2+</sup> release from the endoplasmic reticulum, reactive oxygen species (ROS) generation, mitochondria dysfunction with enhanced expression of Bax protein levels, caspase-3 and caspase-7 activation, suggesting that LAAO-BI causes nephrotoxicity by acting in multiple cell death pathways. LAAO-BI (10 µg/mL) exerts significant effects on the isolated kidney perfusion increasing perfusion pressure and urinary flow and decreasing the glomerular filtration rate and sodium, potassium and chloride tubular transport. Taken together our results suggest that LAAO-BI is responsible for the nephrotoxicity observed in the envenomation by snakebites.

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## Primary cardiac lymphoma in a patient with concomitant renal cancer

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Primary cardiac lymphoma is defined as a non-Hodgkin lymphoma involving the heart and/or pericardium. It is a rare cancer that primarily affects the right heart and in particular the right atrium. By contrast, renal cell carcinoma is a relatively common cancer, which in rare circumstances can metastasize to the heart. It is now known that there is an association between non-Hodgkin lymphoma and renal cell carcinoma, although the underlying mechanisms are not fully understood. The authors present a case of primary cardiac non-Hodgkin lymphoma in a patient with concomitant renal cell carcinoma and explore the possible reasons for this association.

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