HEMOLYSIS: A FATAL COMPLICATION OF ALKAPTONURIA IN SEVERE RENAL FAILURE PATIENTS.

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Introduction

Alkaptonuria (AKU) is a autosomal recessive disorder involving the gene *HGD*, coding for homogentisic acide oxidase. In alkaptonuria patients, deficiency of this enzyme leads to the accumulation of homogentisic acid (HGA) in tissues called ochronosis. Ochronosis is induced by the impossibility to convert HGA into maleylacetoacetic acid in the tyrosine catabolic pathway (Fig 1).

Clinical symptoms include kidney stones, arthritis and joint destruction, pigmentation of cartilages and connective tissues and cardiac valve deterioration, and rarely interstitial nephropathy with pigment deposition leading to chronic renal failure.

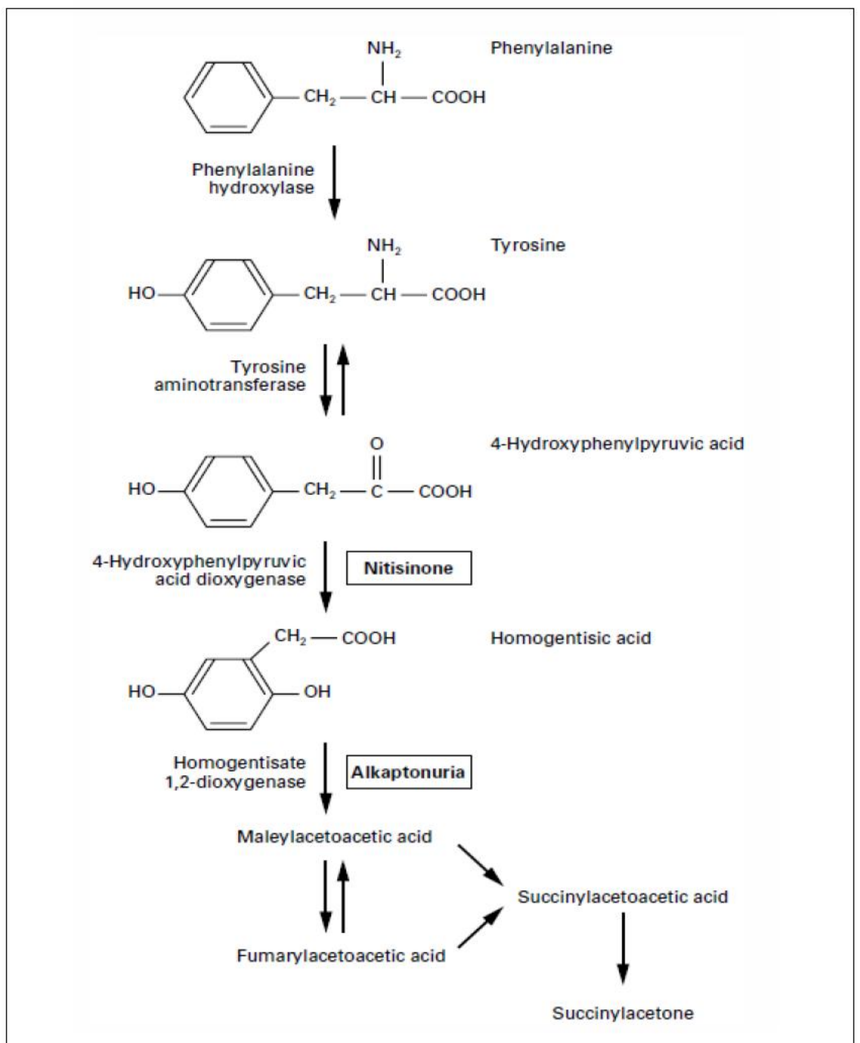

Fig 1: The Tyrosine Catabolic Pathway

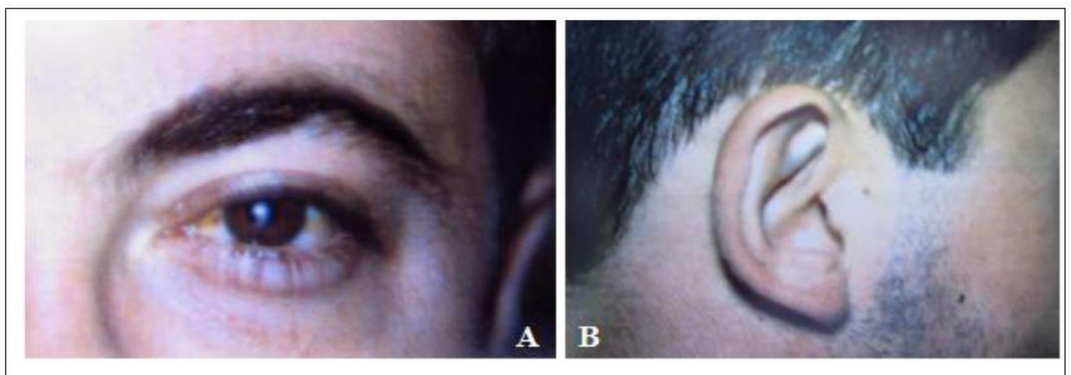

Fig 2: Clinical and histological features of alkaptonuria before acute hemolysis. A: Pigmentation of left ocular sclera secondary to homogentisic acid deposition. B: Pigmentation of right ear cartilage secondary to homogentisic acid deposition.

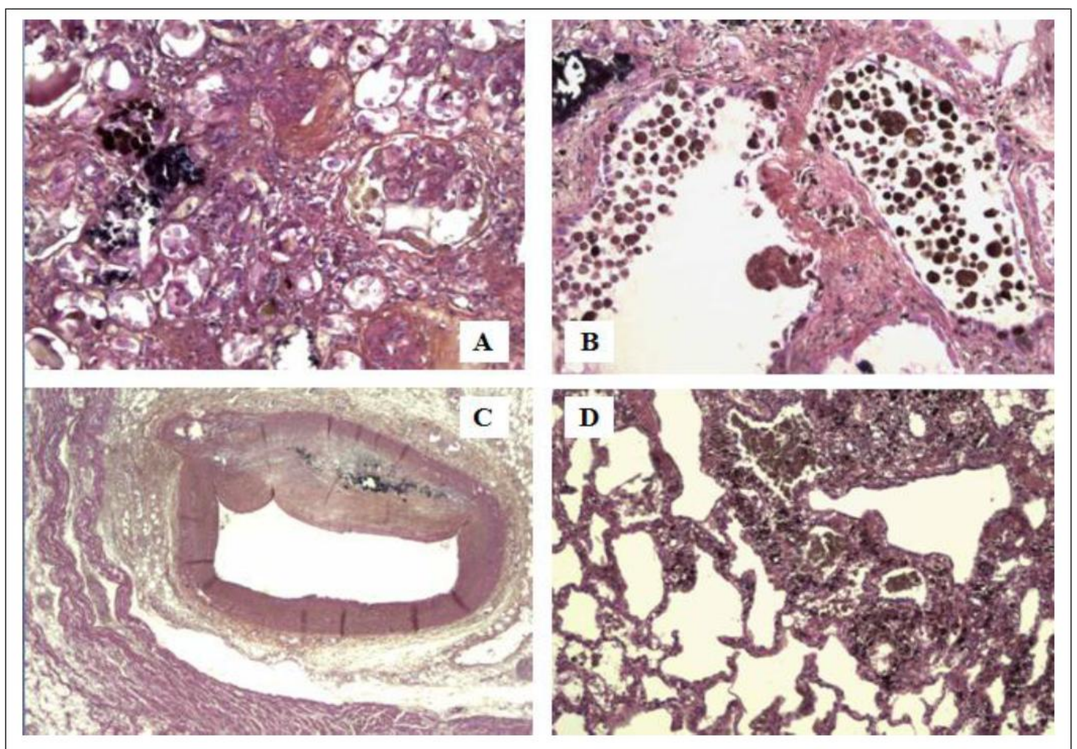

Fig 3: Pathological features of autopsy (HES). A: Tubular pigment casts and interstitial fibrosis in native kidney. B: Dilated tubules with pigmented macrophages in native kidney. C and D: Asymmetric pigment deposition in the wall of the coronary arteries (C) and pulmonary alveoli (D).

Case Report

A 27-year-old man was admitted to the hospital for anemia one month after dialysis was initiated for previous renal transplantation failure following alkaptonuria nephropathy. Molecular studies of the patient's DNA had detected a heterozygous insertionnal substitution (c.198GC>ATT) of the *HGD* gene responsible for a frameshift (p.F10fs). The second mutation was unknown, but parents were both originating from the Venetian region.

At admission, hemoglobin was 30g/L thrombopenia 130G/L. He showed hemolysis with haptoglobin <0.1g/L and inefficient blood transfusions, but no schistocytes. At this time, his skin was green-blue colored all over the body (Fig 2). Patient died of unexplained multiorgan failure before other analysis could be performed. Autopsy was performed but showed no other explanation to death.

Recently it has been described a new symptom occurring in a patient with kidney failure and leading to death: hemolysis (Heng 2010). As mentioned by Heng et al., hemolysis might be induced by high HGA plasma level and from the formation of plasma soluble melanins caused by HGA oxidation. In vitro HGA was found to spontaneously form plasma soluble melanins soon after the beginning of incubation in human blood or plasma at 37°C. In this experimental study, oxidation and polymerization of HGA in the blood was accompanied by hemolysis. The addition of antioxidants significantly delayed oxidation. In our patient, this mechanism may be responsible for hemolysis and organ failure.

CONCLUSIONS:

We report the second case of unexplained hemolysis leading to death in a 27-year old ESRD patient with alkaptonuria. We hypothesize that hemolysis is induced by high HGA plasma level following plasma soluble melanins formation caused by HGA oxidation. In vitro HGA spontaneously form plasma soluble melanins after incubation in human blood or plasma at 37°C. Oxidation and polymerization of HGA in the blood accompanied hemolysis. Thus, AKU is a very dangerous state in patients with renal failure because HGA accumulation and oxidation might induce acute hemolysis. We recommend early renal transplantation in AKU patients with renal failure.

Heng AE, Courbebaisse M, Kemeny JL, Matesan R, Bonniol C, Deteix P, Souweine B. Hemolysis in a patient with alkaptonuria and chronic kidney failure. Am J Kidney Dis 2010 Jul; 56(1):e1-4.

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