CLINICAL CASE

FALLA HEPÁTICA AGUDA DE PROBABLE ETIOLOGÍA METABÓLICA: TIROSINEMIA TIPO I: REPORTE DE CASO Y REVISIÓN DE LA LITERATURA.

ACUTE LIVER FAILURE OF PROBABLE METABOLIC ETIOLOGY: TYROSINEMIA TYPE I: CASE REPORT AND LITERATURE REVIEW.

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RESUMEN

Introducción: La falla hepática aguda es una enfermedad multisistémica infrecuente, pero potencialmente fatal, que se presenta en un niño previamente sano con rápida progresión a la disfunción hepática y falla severa de la síntesis. Las principales causas se pueden agrupar así: infecciosas, metabólicas (tirosinemia, galactosemia),fármacos, vasculares, hepatitis autoinmune, neoplasias e indeterminada. La tirosinemia tipo I (THI) es una enfermedad autosómica recesiva causada por la deficiencia de la enzima fumarilacetoacetato hidrolasa. La THI es una enfermedad rara, se calcula una frecuencia no mayor de 1 caso cada 100.000 recién nacidos vivos en la población mundial. **Caso:** paciente femenina de 5 años al ingreso con datos clínicos de falla hepática aguda de probable etiología metabólica por reporte de paraclínicos y anatomía patológica se sospechó de una Tirosinemia tipo I. **Conclusiones:** El tratamiento consiste en la administración de nitisinona y de forma simultánea se debe instaurar una dieta restringida en

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proteínas. El pronóstico está determinado por el riesgo de carcinoma hepatocelular que aumenta con el retraso del inicio del tratamiento.

PALABRAS CLAVES: falla hepática aguda, tirosinemia, trasplante hepático.

ABSTRACT

Introduction: Acute liver failure is an uncommon but potentially fatal multisystemic disease presenting in a previously healthy child with rapid progression to liver dysfunction and severe synthesis failure. The main causes can be grouped as follows: infectious, metabolic (tyrosinemia, galactosemia), drugs, vascular, autoimmune hepatitis, neoplasms and undetermined. Tyrosinemia type I (THI) is an autosomal recessive disease caused by deficiency of the enzyme fumarylacetoacetate hydrolase. THI is a rare disease, with an estimated frequency of no more than one case per 100,000 live newborns in the world population. **Case:** 5-year-old female patient on admission with clinical data of acute liver failure of probable metabolic etiology by paraclinical report and pathological anatomy was suspected Tyrosinemia type I. **Conclusions:** Treatment consists in the administration of nitisinone, and a protein-restricted diet should be established at the same time. The prognosis is determined by the risk of hepatocellular carcinoma that increases with the delay of treatment initiation.

KEY WORDS: acute liver failure, tyrosinemia, liver transplantation.

INTRODUCTION

Acute liver failure (ALF) is an uncommon but potentially fatal multisystem disease that occurs in a previously healthy child, rapidly progressing to liver dysfunction and severe synthetic failure. The proposed criteria for its definition include: no known chronic liver disease, biochemical evidence of liver involvement, and coagulopathy that does not correct with vitamin K administration, with an INR >1.5 and signs of encephalopathy , or INR >2.0 without encephalopathy (1). The etiology of ALF is influenced by age, geographic location, and socioeconomic development. The main causes can be grouped as follows: infectious (herpes virus and cytomegalovirus), metabolic (tyrosinemia, galactosemia, and Wilson's disease), drug toxicity (mainly acetaminophen), vascular causes, autoimmune hepatitis, neoplasms, and indeterminate cases (ranging from

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18-50%, depending on the facility and access to etiological studies). (2).

Tyrosine is a non-essential amino acid derived from two sources: diet and phenylalanine hydroxylation. In addition to being part of proteins, it is a precursor of DOPA, thyroxine, and melanin. Post-translational modifications of tyrosine residues in proteins through phosphorylation and sulfation play important roles in signal transduction and modulation of protein interactions. Tyrosine is both glucogenic and ketogenic, as its catabolism occurs predominantly in the hepatic cytosol, leading to the formation of fumarate and acetoacetate.

The first step in tyrosine catabolism is its conversion to 4-hydroxyphenylpyruvate by cytosolic tyrosine aminotransferase. Transamination of tyrosine can also occur in the liver and other tissues via mitochondrial aspartate aminotransferase, although this enzyme plays a minor role under normal conditions. The penultimate intermediates in tyrosine catabolism, maleylacetoacetate and fumarylacetoacetate, are reduced to succinylacetoacetate, followed by decarboxylation to succinylacetone. The latter is the most potent known inhibitor of the heme biosynthesis enzyme 5-aminolevulinic acid dehydratase (porphobilinogen synthase). (3).

Five hereditary disorders of tyrosine metabolism are known. Hereditary tyrosinemia type I is characterized by progressive liver disease and renal tubular dysfunction with rickets. Type II tyrosinemia (Richner-Hanhart syndrome) presents with keratitis, blistering lesions on the palms and soles, and neurological complications. Type III tyrosinemia may be asymptomatic or associated with intellectual disability. Other congenital errors in tyrosine metabolism include oculocutaneous albinism caused by melanocyte-specific tyrosinase deficiency (converts tyrosine to DOPA-quinone), tyrosine hydroxylase deficiency (first enzyme in dopamine synthesis from tyrosine), and aromatic L-amino acid decarboxylase deficiency, which also affects tryptophan metabolism. The latter two disorders may be asymptomatic or cause growth retardation and metabolic acidosis in infancy (4).

Tyrosinemia type I (HTI) is an autosomal recessive disorder caused by deficiency of the enzyme fumarylacetoacetate hydrolase (FAH), mainly expressed in the liver and kidneys. The compounds immediately upstream of the FAH reaction—maleylacetoacetate (MAA) and fumarylacetoacetate (FAA)—and their derivatives, succinylacetone (SA) and

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succinylacetoacetate (SAA), accumulate and have significant pathogenic effects. The effects of FAA and SAA occur only in the cells where they are produced; they are not found in patients' body fluids. In contrast, SA and SAA are easily detected in plasma and urine. FAA, MAA, and SA alter sulfhydryl metabolism by forming glutathione adducts, making cells susceptible to damage from free radicals (5) Sulfhydryl metabolism disruption may also cause secondary deficiency of two other liver enzymes: 4-hydroxyphenylpyruvate dioxygenase and methionine adenosyltransferase, leading to elevated tyrosine and methionine levels. SA is a potent inhibitor of 5-aminolevulinic acid dehydratase (5-ALA dehydratase) (6).

5-ALA, a neurotoxic compound, accumulates and is excreted at high levels in patients with HTI and is believed to cause acute neurological crises during decompensation. SA is also known to impair renal tubular function, heme synthesis, and immune function (7).

HTI is a rare disease, with a global incidence of no more than 1 case per 100,000 live births. Incidence is higher in some regions, especially Quebec, Canada, where it occurs in 1 in 1,800 live births and 1 in 25 people are carriers of the IVS12+5G>A mutation (8).

Clinical manifestations of HTI are highly variable and can appear at any time from the neonatal period to adulthood. There is clinical heterogeneity even among family members. Clinically, HTI can be classified by age of symptom onset, which generally correlates with disease severity: an acute form before 6 months of age (rarely within the first two weeks) with acute liver failure; a subacute form between six months and one year with liver disease, growth retardation, coagulopathy, hepatosplenomegaly, rickets, and hypotonia; and a more chronic form after one year with chronic liver disease, renal disease, rickets, cardiomyopathy, and/or a porphyria-like syndrome (9).

The liver is the main organ affected in HTI and is a major source of morbidity and mortality. Liver disease may present as acute liver failure, cirrhosis, or hepatocellular carcinoma (HCC), and these may occur in the same patient. The most severe forms of HTI occur in the first weeks of life with vomiting, diarrhea, hemorrhagic diathesis, hepatomegaly, jaundice, hypoglycemia, edema, and ascites. Marked hepatic synthetic dysfunction is characteristic, especially coagulopathy, in contrast to other liver function tests. Sepsis is common, and hypophosphatemic rickets due to renal tubular dysfunction may occur. Chronic liver disease leading to

cirrhosis occurs in most HTI patients, either as a late complication in early-onset survivors or as an initial feature of later-onset forms. Cirrhosis is typically mixed micro- and macronodular, with varying degrees of steatosis. (10,11).

Most patients have some degree of renal dysfunction at presentation, from mild tubular dysfunction to renal failure. Renal abnormalities include metabolic acidosis, elevated alkaline phosphatase, hypophosphatemia, hypokalemia, and findings in urine such as glucosuria, phosphaturia, bicarbonaturia, hypercalciuria, uricosuria, low ammonia production, and urinary pH below 6, with low-density urine due to impaired concentrating ability. Proximal tubular disease is common and may worsen during hepatic crises. Hypophosphatemic rickets is the most common manifestation of proximal tubulopathy, though aminoaciduria, renal tubular acidosis, and glucosuria may also be present.

Acute neurological crises can occur at any age. These usually follow minor infections accompanied by anorexia and vomiting and occur in two phases: an active phase lasting 1 to 7 days with painful paresthesia and autonomic signs possibly progressing to paralysis, followed by a recovery phase lasting days to months. Complications include seizures, severe hyperextension, self-injury, respiratory paralysis, and death (12) .

Other clinical manifestations include cardiomyopathy, occasionally found incidentally but potentially clinically significant, and clinically significant hyperinsulinism associated with pancreatic cell hypertrophy (13).

Diagnosis is based on identifying elevated levels of succinylacetone (SA) in dried blood, plasma, or urine, which is a pathognomonic metabolite. Other metabolic abnormalities suggesting the diagnosis include elevated urinary levels of tyrosine, methionine, phenylalanine, and 4-hydroxyphenyl derivatives; prolonged prothrombin time; and elevated transaminases and alpha-fetoprotein. Normocytic anemia, leukocytosis, and thrombocytosis may also be present (14).

Imaging studies (ultrasound, CT, or MRI) show changes consistent with chronic hepatitis that may progress to cirrhosis and, with longer evolution, hepatocellular carcinoma.

Histopathological liver findings include lobular fibrosis, ductal proliferation, cholestasis, necrotic bridges forming nodules, mixed infiltrate, steatosis, and micro- or macronodular cirrhosis. (15).

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Newborn metabolic screening includes measuring SA as a highly sensitive and specific marker. It can also be detected through chorionic villus sampling if the mutation has been previously identified in the family.

HTI is inherited as an autosomal recessive trait. The FAH gene is located on 15q23-q25, and nearly 100 mutations have been described. The most common mutation, c.1062+5G>A, is found in about 25% of alleles worldwide and is the predominant mutation in the French Canadian population, representing more than 90% of alleles. Another mutation, c.554-1G>T, is found in around 60% of alleles in patients from the Mediterranean region. Other FAH mutations are common in certain ethnic groups: W262X in Finns, D233V in Turks, and Q64H in Pakistanis. There is no clear genotype-phenotype correlation; spontaneous correction of the mutation within regenerative nodules may influence the clinical phenotype. (15,16).

Treatment is based on the administration of nitisinone, also known as NTBC (2-nitro-4-(trifluoromethyl)benzoyl-1,3-cyclohexanedione), in combination with a diet restricted in tyrosine and phenylalanine. NTBC blocks the early steps of tyrosine degradation, preventing the formation of toxic metabolites like FAA, MAA, and SA. Consequently, levels of tyrosine, 4-hydroxyphenylpyruvate, and its derivatives increase. NTBC acts within hours of administration and has a long half-life of approximately 54 hours. In patients presenting with acute liver failure, clinical improvement is observed in over 90% of cases, often reflected by an improvement in prothrombin time within a few days of starting treatment. Other biochemical liver parameters may take longer to normalize; alpha-fetoprotein levels should decrease logarithmically but may take several months to normalize after initiating treatment. The initial recommended dose of NTBC is 1–2 mg/kg body weight per day. Individual dose adjustments are based on biochemical response, aiming for a plasma nitisinone concentration >50 µmol/L or a whole blood concentration of 20–40 µmol/L. (17,18).

Dietary restriction of phenylalanine and tyrosine is necessary to prevent the adverse effects of elevated tyrosine levels. The therapeutic goal is to maintain tyrosine levels between 200 and 400 µmol/L and phenylalanine levels >30 µmol/L through a combination of protein-restricted diets and amino acid mixtures free of phenylalanine and tyrosine. (19).

It should be noted that up to 10% of patients presenting with acute liver failure do not respond to NTBC treatment. In such cases, liver

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transplantation becomes the definitive treatment. Reported side effects of NTBC include thrombocytopenia, leukopenia, neutropenia, eye pain, conjunctivitis, photophobia, corneal opacities, keratitis, pruritus, and exfoliative dermatitis.

Follow-up of patients on nitisinone should include regular monitoring of full liver function tests, NTBC levels, amino acid profiles, renal function tests, urinary SA levels, and alpha-fetoprotein levels every 3 months, along with liver imaging via ultrasound every 6 months.

Liver transplantation is reserved for patients with acute liver failure who do not respond to NTBC and for those with suspected or confirmed hepatocellular carcinoma (20,21).

REPORTED CASE.

A 5-year-old female patient, with no prior pathological history, presented with a clinical picture of five days' evolution, characterized by severe diffuse colicky abdominal pain, asthenia, adynamia, prostration, and drowsiness. On physical examination, she was found to be in fair general condition, with generalized pallor, somnolence, and abdominal pain scored at 10/10 on the Visual Analog Scale (VAS) across all quadrants, accompanied by abdominal guarding and edema of the eyelids and lower limbs. Her vital signs were as follows: blood pressure (BP) 105/66 mmHg, heart rate (HR) 105 beats per minute, and body mass index (BMI) 16.98 kg/m². Given the clinical suspicion of appendicitis, supported by a Samuel score of 8 points, an exploratory laparoscopy was performed.

Intraoperative findings included dilated small bowel loops with segmental inflammation of the intestinal wall, a yellowish, nodular, inflamed liver (Figure 1), turbid peritoneal fluid in the pouch of Douglas, and an edematous subhepatic appendix. An appendectomy and a wedge liver biopsy were carried out without complications.

At admission, laboratory tests revealed mild normocytic hypochromic anemia on the complete blood count, with a normal C-reactive protein (CRP) level. Arterial blood gas analysis showed severe metabolic acidosis. Liver function tests were notable for hypertransaminasemia, hypoalbuminemia, cholestasis, coagulopathy, and hypofibrinogenemia. Pediatric gastroenterology ordered extended diagnostic testing including infectious, metabolic, and autoimmune panels.

Infectious serologies were negative for Herpes simplex types I and II,

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cytomegalovirus, toxoplasma (IgM and IgG), dengue (IgM), hepatitis A, leptospira, hepatitis B surface antigen (HBsAg), and anti-hepatitis C virus (anti-HCV); the Venereal Disease Research Laboratory (VDRL) test was non-reactive, HIV testing was negative, and a thick blood smear was also negative. Autoimmune studies showed negative results for antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-smooth muscle antibodies, and anti-soluble liver antigen.

Imaging studies revealed a normal portal Doppler and normal renal ultrasound. Abdominal computed tomography (CT) demonstrated decreased liver density without space-occupying lesions. Cranial CT revealed bilateral hyperdense parietal lesions measuring 12 mm, suggestive of intracerebral hemorrhage.

Liver function tests reported the following values: albumin 3.01 g/dL, alkaline phosphatase 1380 U/L, prothrombin time (PT) with no coagulation at 360 seconds, activated partial thromboplastin time (aPTT) 79 seconds, fibrinogen 55 mg/dL, aspartate aminotransferase (AST) 994 U/L, alanine aminotransferase (ALT) 875 U/L, total bilirubin 8.1 mg/dL, direct bilirubin 3.38 mg/dL, indirect bilirubin 4.79 mg/dL, and gamma-glutamyl transferase (GGT) 35 U/L.

During her clinical course, the patient required supplemental oxygen via nasal cannula at a flow rate of 3 L/min. She was given vitamin K every 12 hours and an osmotic laxative (lactulose) at a dose of 1 mg/kg/dose every 8 hours. Vasoactive support was initiated with adrenaline, norepinephrine, and vasopressin. Empirical antibiotic therapy with meropenem was started. Due to shock refractory to catecholamines, vasopressin was maintained. As active bleeding developed—manifesting as epistaxis, hematemesis, hematuria, and melena—fresh frozen plasma and cryoprecipitate transfusions were administered. On the third day of hospitalization, the patient required mechanical ventilation due to ventilatory failure. She was transferred to the Pediatric Intensive Care Unit (PICU) on the fourth day. A respiratory FilmArray panel detected the presence of parainfluenza virus. Vasoactive support was continued with the addition of milrinone, and linezolid was incorporated into the antimicrobial regimen. Although plasmapheresis was considered due to worsening coagulopathy and persistent bleeding, it was not performed because of hemodynamic instability. The patient was evaluated by a multidisciplinary team including pediatric gastroenterology, infectious diseases, nephrology, neurosurgery, pediatric surgery, and genetics. Forty-eight hours after PICU admission, the

patient experienced neurological deterioration, presenting a Glasgow Coma Scale (GCS) score of 3/15 and absence of brainstem and deep tendon reflexes. On the seventh day of her stay in the PICU, the patient died. Postmortem studies included histopathology, plasma ammonia, ceruloplasmin, urinary short- and medium-chain organic acids, and serum amino acids. Results showed a markedly elevated ammonia level at 463 µmol/L, ferritin at 1000 ng/mL, and ceruloplasmin at 17 mg/dL. Urinary organic acid analysis revealed elevated levels of 4-hydroxyphenyl-lactic acid, 4-hydroxyphenylpyruvic acid, 3-phenyl-lactic acid, and N-acetyl-tyrosine. Serum amino acid testing showed tyrosine at 389 µmol/L and methionine at 113 µmol/L.

Pathological Anatomy of Liver Biopsy: A portal tract is observed with infiltrate extending toward and connecting with a second portal tract on both the right and left sides, delineating three nodules of hepatocytes separated by fibrotic and inflammatory infiltrate—above, to the right, and to the left—with hepatocytes showing steatosis (Figure 2). A portal tract is seen with venule and bile ductule accompanied by fibrosis, lymphocytes, plasma cells, and hepatocytes displaying damage and fat macrovesicles (Figure 3). With trichrome staining, marked fibrosis is observed in the portal tract, involving the artery, vein, and bile ductules (Figure 4). In PAS staining, one portal tract and a central vein are identified, along with fibrosis and necrosis in hepatocytes from zones 1 and 3, and steatosis (Figure 5).

With reticulin staining, golden-colored collagen fibers are seen, indicating fibrosis in the portal tract and delimiting lobules of hepatocytes (Figure 6). In hematoxylin and eosin (H&E) staining, hepatocytes with micro- and macrovesicular vacuoles are noted, as well as necrotic changes such as pyknosis, karyolysis, and severe inflammatory infiltrate on the right (Figure 7).

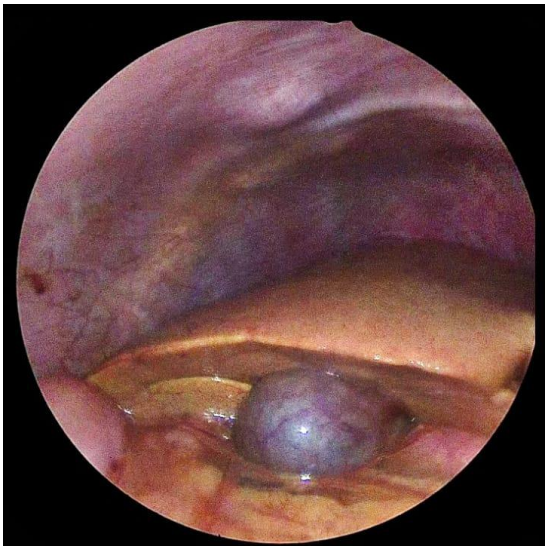

Figure 1. Microscopic liver

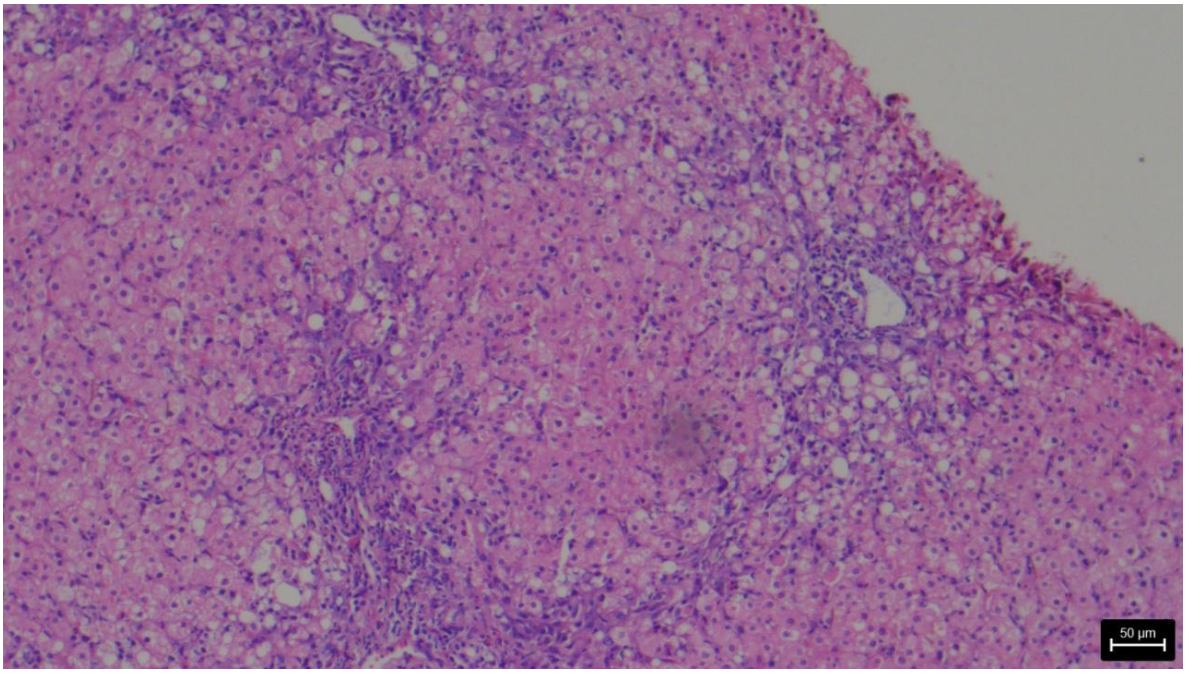

Figure 2. Inflammatory infiltrate and fibrosis

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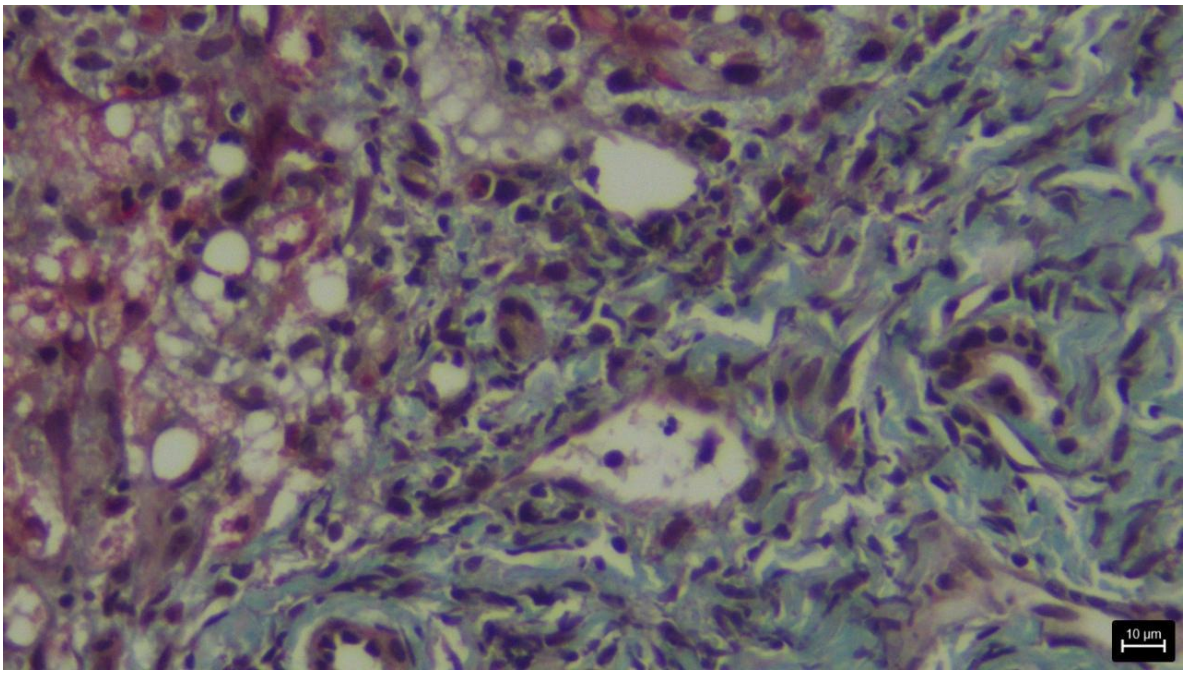

Figure 3: portal space with venule and ductule with fibrosis

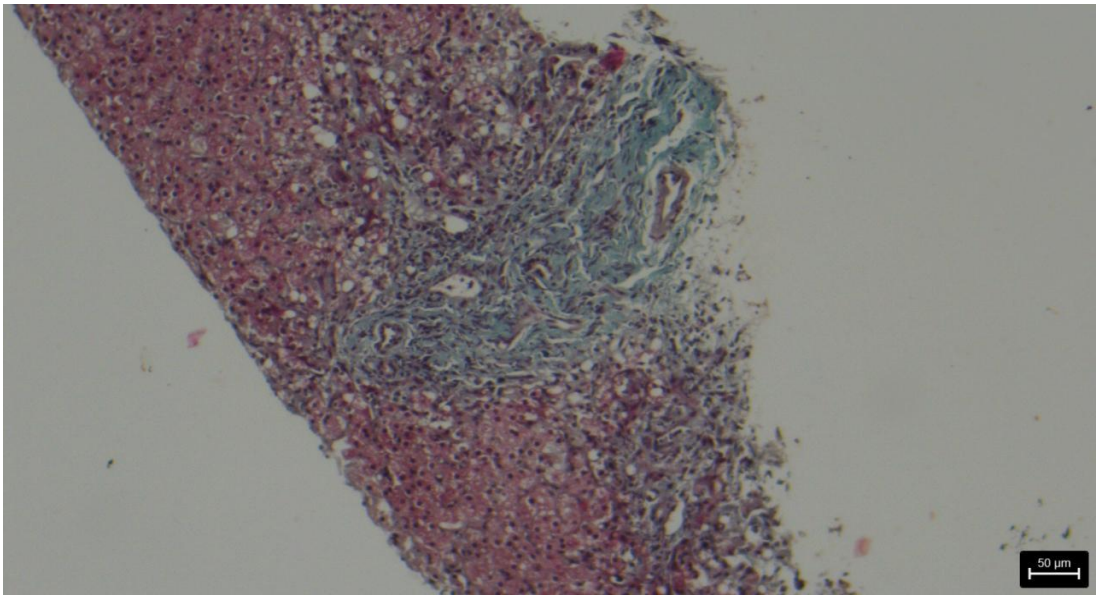

Figure 4: Trichrome staining: blue is connective tissue representing fibrosis and red is hepatocytes.

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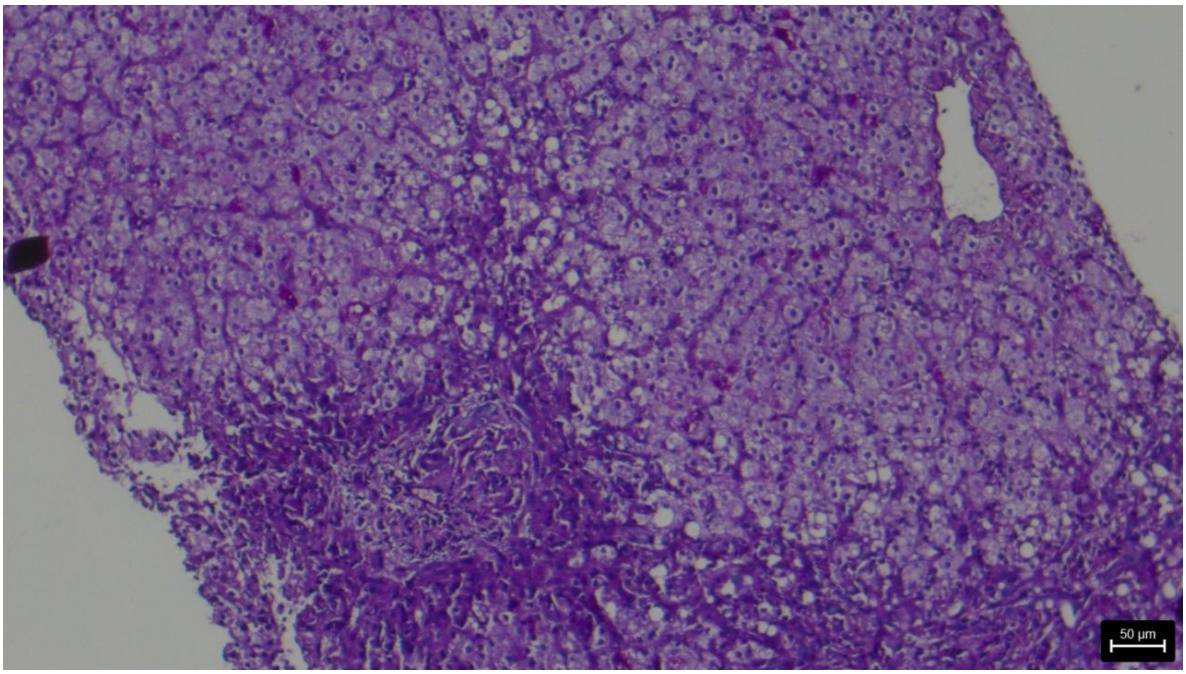

Figure 5 : PAS staining

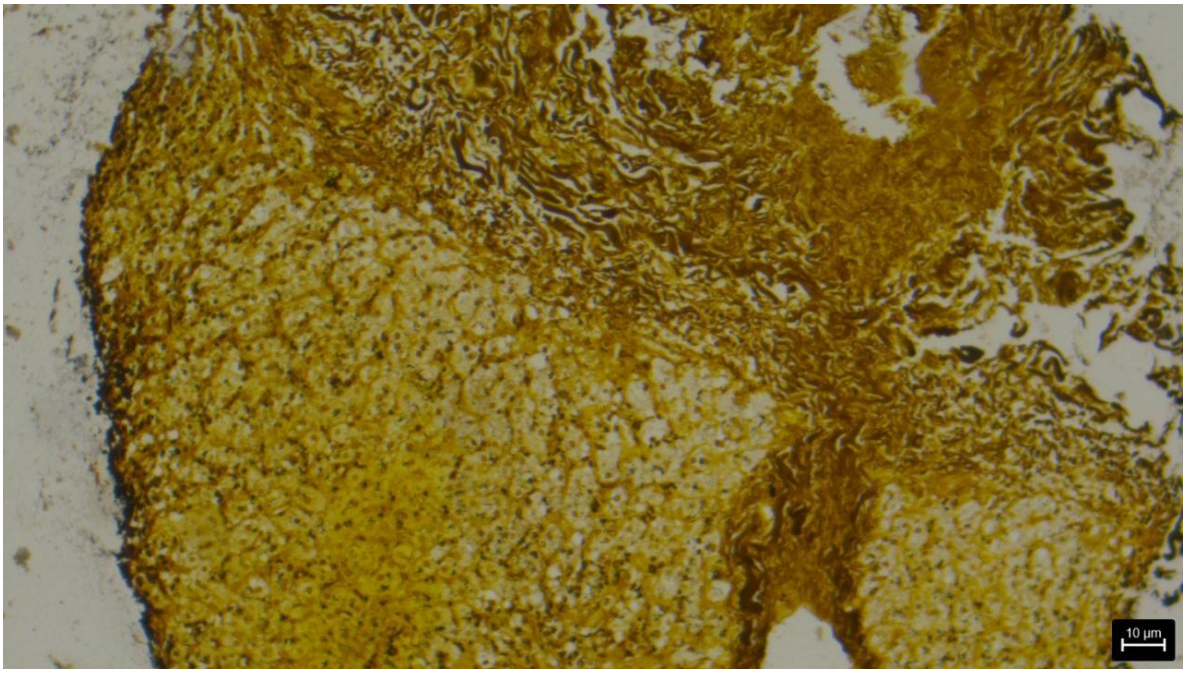

Figure 6.RET staining.

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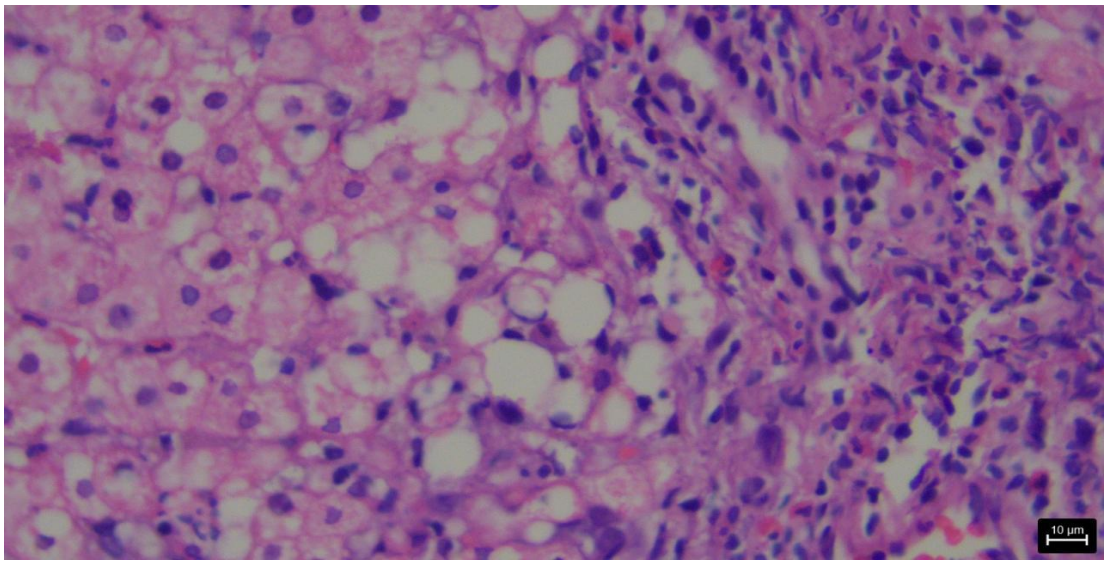

Figure 7: Hematoxylin-eosin staining: hepatocytes with micro and macro vacuole, necrotic changes such as pyknosis, karyolysis and severe right inflammatory infiltrate.

DISCUSSION.

Liver disease in hereditary tyrosinemia type I (HTI) may present as acute liver failure (ALF), cirrhosis, or hepatocellular carcinoma (HCC); all three conditions can occur in the same patient. ALF may be the initial manifestation or may develop later. Sepsis is common and may be associated with early-onset hypophosphatemic bone disease secondary to renal tubular dysfunction. Cirrhosis is typically mixed (micro- and macronodular) with a variable degree of steatosis (20).

In our patient, we considered the possibility of tyrosinemia type I due to hepatic dysfunction with severe impairment of hepatic synthesis—especially the presence of coagulopathy—elevated alkaline phosphatase, high ammonia levels, increased urinary excretion of 4-hydroxyphenyl-lactic acid, 4-hydroxyphenylpyruvic acid, 3-phenyl-lactic acid, and N-acetyl-tyrosine, as well as elevated plasma levels of tyrosine and methionine, and histopathological findings of steatohepatitis and severe fibrosis. However, no enzymatic or genetic studies were performed to confirm the diagnosis.

CONCLUSION.

The liver is the most severely affected target organ in HTI.

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Pathophysiologically, fumarylacetoacetate (FAA) is described as a cytotoxic compound that triggers apoptosis in hepatocytes and renal tubular epithelial cells and plays a direct role in hepatic carcinogenesis. Based on the above, the presence of renal tubular dysfunction in a patient with hepatocellular involvement should prompt investigation for HTI. However, other differential diagnoses such as glycogen storage disease type I, Wilson's disease, galactosemia, and hereditary fructose intolerance should also be considered.

Tyrosinemia is a metabolic disorder that may initially present as acute liver failure and represents a treatable etiology. Treatment is based on oral administration of nitisinone (NTBC) at a dose of 1–2 mg/kg per day, which constitutes an excellent short- and medium-term therapeutic alternative to liver transplantation, especially when combined with a protein-restricted diet. Liver transplantation (LT) should be considered in patients with ALF who do not respond to treatment with nitisinone, and in those with suspected or confirmed hepatocellular carcinoma. LT can prevent the development of hepatocellular carcinoma, correct metabolic abnormalities, and normalize liver function.

Genetic counseling should be offered to the parents regarding the mode of inheritance of the disease and the risk of having additional children with this condition, given its autosomal recessive transmission, and the 25% recurrence risk in future pregnancies (22–24).

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