**УДК: 616.36:06+618.3**

# CLINICO-MORPHOLOGICAL CHARACTERISTICS OF ACUTE FATTY LIVER OF PREGNANCY

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***Abstract***

**Aim of the study.** *To study the clinical and morphological changes of fatal liver damage in acute fatty hepatosis of the liver (AFH) in pregnant women.*

**Materials and methods.** *A 26-year-old pregnant woman with gestosis, anemia, and duodenal ulcer was taken. At the 24th week of pregnancy, the first pre-icteric stage of AFLP was diagnosed against the background of gradually developing gestosis. Clinically, symptoms such as weakness, lethargy, nausea, vomiting, abdominal discomfort and pain were observed. At the 25th week of pregnancy, the next stage of AFLP developed, characterized by severe jaundice, nausea, repeated gastrointestinal bleeding, post-hemorrhagic anemia, and disseminated intravascular coagulation syndrome (DIC), which ultimately led to death. Histological sections were deparaffinized and stained with hematoxylin and eosin for microscopic examination.*

**Conclusion.** *This study presents a clinico-morphological analysis based on autopsy of a mother who died of acute fatty liver disease (AFLD) during pregnancy. In the pre-icteric stage, clinical signs such as weakness, fatigue, nausea, vomiting, abdominal discomfort and pain were associated with diffuse microvesicular fat accumulation. In the second (icteric) stage, pathological morphological changes in the liver - diffuse fatty degeneration, necrobiota of nuclear structures, sinusoidal congestion and focal diapedetic hemorrhages - were more pronounced. In this stage, degenerative and necrotic processes spread to other parenchymal organs, for example, microvesicular fatty degeneration of the renal tubular epithelium and the subendocardial zone of the myocardium.*

***Keywords:*** *pregnancy, gestosis, hepatosis, asymptomatic fatty liver degeneration, maternal mortality.*

***Annotatsiya***

**Tadqiqot maqsadi.** *Homilador ayollarda jigarning o'tkir yog'li gepatozi (HJO'YoG)da o'limga olib keladigan jigar zararlanishining klinik-morfologik o'zgarishlarini o'rganish.*

**Materiallar va usullar.** *Gestoz, anemiya va o'n ikki barmoqli ichakning oshqozon yarasining kasalligi bilan og'rigan 26 yoshli homilador ayol olingan. Homiladorlikning 24-haftasida asta-sekin rivojlanayotgan gestoz fonida AFLP ning birinchi pre-ikterik bosqichi*

*tashxisi qo'yilgan. Klinik jihatdan zaiflik, letargiya, ko'ngil aynishi, qusish, qorin bo'shlig'idagi noqulaylik va og'riq kabi alomatlar kuzatildi. Homiladorlikning 25-haftasida AFLP ning keyingi bosqichi rivojlanib, og'ir sariqlik, ko'ngil aynishi, takroriy oshqozon-ichakdan qon ketish, post-gemorragik anemiya va tarqalgan tomir ichidagi koagulyatsiya sindromi (DIC) bilan tavsiflanadi, natijada o'limga olib keldi. Gistologik bo'limlar deparafinizatsiya qilindi va mikroskopik tekshirish uchun gematoksilin va eozin bilan bo'yaldi.* **Xulosa.** *Ushbu ishda homiladorlik paytida o‘tkir yog‘li jigar distrofiyasi (O‘YJD) natijasida vafot etgan ona autopsiyasi asosida o'tkazilgan kliniko-morfologik tahlil taqdim etilgan. Pre-ikterik bosqichda kuchsizlanish, holsizlik, ko'ngil aynishi, qayt qilish, qorinning noqulayligi va og‘rig‘i kabi klinik belgilar diffuz mikrovezikulyar yog‘ to‘planishi bilan bog‘liq edi. Ikkinchi (ikterik) bosqichda jigar patologik morfologik o‘zgarishlari – diffuz yog‘li degeneratsiya, yadroviy tuzilmalar nekrobioti, sinusodal kongestsiya va fokal diapedetik qon ketishlar ko‘proq aniqlangan. Bu bosqichda degenerativ va nekrotik jarayonlar boshqa parenximatoz organlarga, masalan, buyrak naycha epitelining mikrovezikulyar yog‘li degeneratsiyasi va miokardiumning subendokardial zonasiga tarqalgan.* ***Kalit so‘zlar:*** *homiladorlik, gestoz, gepatoz, simptomsiz yog‘li jigar degeneratsiyasi, maternal mortalitet.*

***Аннотация***.

**Цель исследования.** *Изучить клинико-морфологические изменения фатального поражения печени при остром жировом гепатозе печени (ОЖГП) у беременных.*

**Материалы и методы.** *Взята беременная женщина 26 лет с гестозом, анемией и язвой двенадцатиперстной кишки. На 24-й неделе беременности диагностирована первая преджелтушная стадия ОЖГП на фоне постепенно развивающегося гестоза. Клинически наблюдались такие симптомы, как слабость, вялость, тошнота, рвота, дискомфорт в животе и боли. На 25-й неделе беременности развилась следующая стадия ОЖГП, характеризующаяся выраженной желтухой, тошнотой, повторными желудочно-кишечными кровотечениями, постгеморрагической анемией и синдромом диссеминированного внутрисосудистого свертывания (ДВС), что в итоге привело к летальному исходу. Гистологические срезы депарафинировали и окрашивали гематоксилином и эозином для микроскопического исследования.*

**Заключение.** *В данной работе представлен клинико-морфологический анализ, основанный на аутопсии матери, умершей от острой жировой болезни печени (ОЖБП) во время беременности. В преджелтушной стадии такие клинические признаки, как слабость, утомляемость, тошнота, рвота, дискомфорт в животе и боли, были связаны с диффузным микровезикулярным накоплением жира. Во второй (желтушной) стадии патологические морфологические изменения в печени - диффузная жировая дистрофия, некробиота ядерных структур, синусоидальное полнокровие и очаговые диапедезные кровоизлияния - были более выражены. В этой стадии дегенеративные и некротические процессы распространялись на другие паренхиматозные органы, например, микровезикулярная жировая дистрофия эпителия почечных канальцев и субэндокардиальной зоны миокарда.*

***Ключевые слова:*** *беременность, гестоз, гепатоз, бессимптомная жировая дистрофия печени, материнская смертность.*

## Introduction.

*Acute fatty liver of pregnancy (AFLP) was first diagnosed in a deceased postpartum woman in 1857. Subsequently additional cases were sporadically reported, often confused with viral hepatitis or preeclampsia-related liver disease. In 1940, H.L. Sheehan described AFLP as a distinct nosological entity, naming it "acute yellow obstetric atrophy of the liver" and providing a detailed characterization of the disease [1,6]. The Swansea criteria, a diagnostic tool, was later developed to assist in the clinical diagnosis of AFLP.The mortality rate of AFLP remains extremely high, reaching 90–100%. This condition is classified as a rare pregnancy-related pathology, occurring in approximately 1 in 13,328 deliveries [3,4].*

*The etiology and pathogenesis of AFLP remain poorly understood. According to most researchers, AFLP is classified as a mitochondrial cytopathy [2,5,7], where fatty degeneration of the liver is a manifestation of systemic mitochondrial dysfunction affecting multiple organs, including the kidneys, muscles, nervous system, pancreas, and heart. It is well known that mitochondria are the primary sites for energy conversion and accumulation through protein catabolism, while carbohydrate breakdown does not occur. This fundamental organelle plays a crucial role in cellular metabolism, especially in tissues with high energy demands such as the liver, heart, skeletal muscle, and placenta during pregnancy. Mitochondria facilitate the breakdown of fatty acids, amino acids, and pyruvate into usable energy via oxidative pathways.*

*Oxidative phosphorylation in mitochondria is coupled with fatty acid oxidation and ATP synthesis, mediated by specific enzymes, such as 3-hydroxyacyl-CoA dehydrogenase. This enzyme is a key component of the mitochondrial trifunctional protein (MTP) complex involved in the β-oxidation of long-chain fatty acids. During pregnancy, the increased lipid mobilization from maternal adipose tissue results in elevated fatty acid flux, placing a higher metabolic load on mitochondrial pathways.*

*There is a theory suggesting that genetic deficiencies in these enzymes underlie AFLP and other mitochondrial cytopathies. This concept is supported by the discovery that defects in mitochondrial β-oxidation impair the liver's ability to process fatty acids, leading to microvesicular steatosis, hepatocellular injury, and systemic metabolic disruption.*

*Genetic studies conducted on women with AFLP and their spouses have confirmed that heterozygous women carrying mutations in genes responsible for 3-hydroxyacyl-CoA dehydrogenase synthesis are at risk of developing AFLP. In many of these cases, the fetus is found to be homozygous for mutations in the HADHA or HADHB genes encoding subunits of the MTP complex. The accumulation of unmetabolized fatty acid intermediates in the maternal circulation, derived from the fetus, contributes to hepatotoxicity and hepatic failure. This maternal-fetal interaction highlights the unique pathophysiology of AFLP as a metabolic "double-hit" syndrome —where maternal heterozygosity and fetal homozygosity synergistically trigger disease onset.*

*This study aims to conduct a clinico-morphological investigation of an autopsy case of maternal mortality due to AFLP.*

**Materials and Methods.**

*The subject was a 26-year-old pregnant woman who suffered from gestosis, anemia, and peptic ulcer disease of the duodenum. At the 24th week of pregnancy, the first pre-icteric stage of AFLP was diagnosed against the background of slowly progressing gestosis. Clinically, symptoms such as weakness, lethargy, nausea, vomiting, abdominal discomfort, and pain were observed. At the 25th week of pregnancy, the next stage of AFLP developed, characterized by severe jaundice, heartburn, recurrent gastrointestinal bleeding, post-hemorrhagic anemia, and disseminated intravascular coagulation (DIC) syndrome, which ultimately led to death. Autopsy findings included pallor, dull skin, multiple petechial hemorrhages in the skin, mucous, and serous membranes, and widespread DIC syndrome with multiple thrombotic occlusions in small blood vessels. Tissue samples (2×2 cm) were excised and fixed in 10% neutral formalin. Following dehydration in ethanol solutions of increasing concentration, the samples were embedded in*

*paraffin. Histological sections were deparaffinized and stained with hematoxylin and eosin for microscopic examination.*

**Results.**

*We present an autopsy case of maternal mortality with clinically and morphologically confirmed AFLP, which developed at the 26th week of pregnancy [9].*

*Pre-Icteric Phase (24th Week of Pregnancy): The patient exhibited progressive weakness, lethargy, nausea, vomiting, abdominal discomfort, and pain. These nonspecific symptoms, while common in various gestational conditions, may reflect early hepatic dysfunction and impaired metabolic regulation. During this phase, the subtle onset of gastrointestinal and constitutional symptoms can delay clinical recognition, especially in the absence of jaundice or laboratory abnormalities.*

*Autopsy findings supported these clinical manifestations, revealing erosions and ulcerations in the mucosa of the esophagus, stomach, and duodenum. These lesions are likely the result of persistent vomiting, metabolic stress, and systemic inflammation, which compromise mucosal integrity. Additionally, impaired hepatic detoxification and altered prostaglandin metabolism may have contributed to mucosal ischemia and ulceration, commonly seen in severe systemic illness. The presence of upper gastrointestinal erosions in the pre-icteric phase serves as an early pathological marker of multi-organ involvement and the evolving severity of AFLP.*

*Icteric Phase (25th Week of Pregnancy): At this stage, the patient developed severe jaundice. The appearance of jaundice marks a critical clinical turning point, signifying hepatocellular dysfunction and impaired bilirubin clearance due to compromised hepatic metabolism. Concurrently, elevated serum transaminases, bilirubin, and prothrombin time are typically observed, although values may vary depending on the stage of hepatic injury.*

*Heartburn reached its peak, often culminating in vomiting with "coffee-ground" content. Hematin-stained emesis is a key indicator of upper gastrointestinal bleeding, which should raise suspicion of pregnancy-related hepatic pathology. This bleeding likely results from stress-induced mucosal damage, compounded by coagulopathy and portal hypertension associated with hepatic insufficiency. The presence of gastrointestinal bleeding in this phase underscores the systemic nature of AFLP and the critical need for rapid stabilization and delivery.*

*As the disease progressed, the patient experienced worsening hepatic failure, encephalopathy, and loss of consciousness. Hepatic encephalopathy is a hallmark of advanced liver dysfunction and results from the accumulation of neurotoxins—primarily ammonia—that are normally detoxified by the liver. Neurological decline is frequently accompanied by asterixis, confusion, and eventually coma, necessitating urgent transfer to intensive care and multidisciplinary management.*

*Laboratory tests revealed leukocytosis, thrombocytopenia, and reductions in hemoglobin and erythrocyte counts. These hematological abnormalities are reflective of systemic inflammatory response, bone marrow suppression, and possible disseminated intravascular coagulation (DIC), which is frequently seen in severe AFLP. Thrombocytopenia may also be worsened by splenic sequestration and microangiopathy.*

*Biochemical analysis demonstrated characteristic markers of mitochondrial cytopathy, including hypoglycemia due to Krebs cycle disruption, hyperammonemia, elevated uric acid levels, and metabolic acidosis. These findings indicate a profound failure in cellular energy production and impaired hepatic clearance functions. Hypoglycemia arises from both decreased gluconeogenesis and increased peripheral utilization, while hyperammonemia reflects urea cycle failure. Elevated uric acid and lactic acidosis further reflect oxidative stress and mitochondrial overload, providing biochemical evidence for the mitochondrial dysfunction that underlies AFLP pathogenesis.*

*Macroscopic Findings. The liver was enlarged, weighing 1,760 g, with a soft consistency. The external surface and cut section displayed an ochre-yellow color with a fine nutmeg-like pattern. (Figure 1A and Figure 1B)*

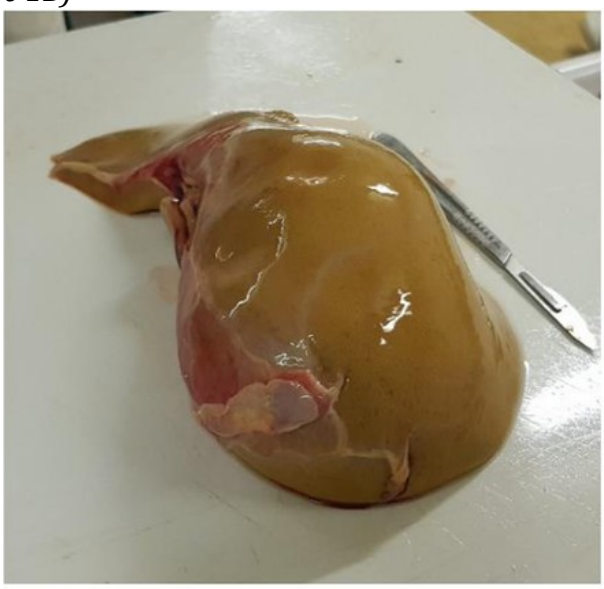

*Figure 1A. Macroscopic Image of liver. The external view.*

*Figure1B. Macroscopic Image of liver. The cut section*

*Microscopic Findings. Histological examination revealed swollen hepatocytes with microvesicular and macrovesicular lipid droplets, while nuclei remained centrally located. The hepatic lobular architecture, including portal tracts and hepatic cords, was preserved. (Figure 2)*

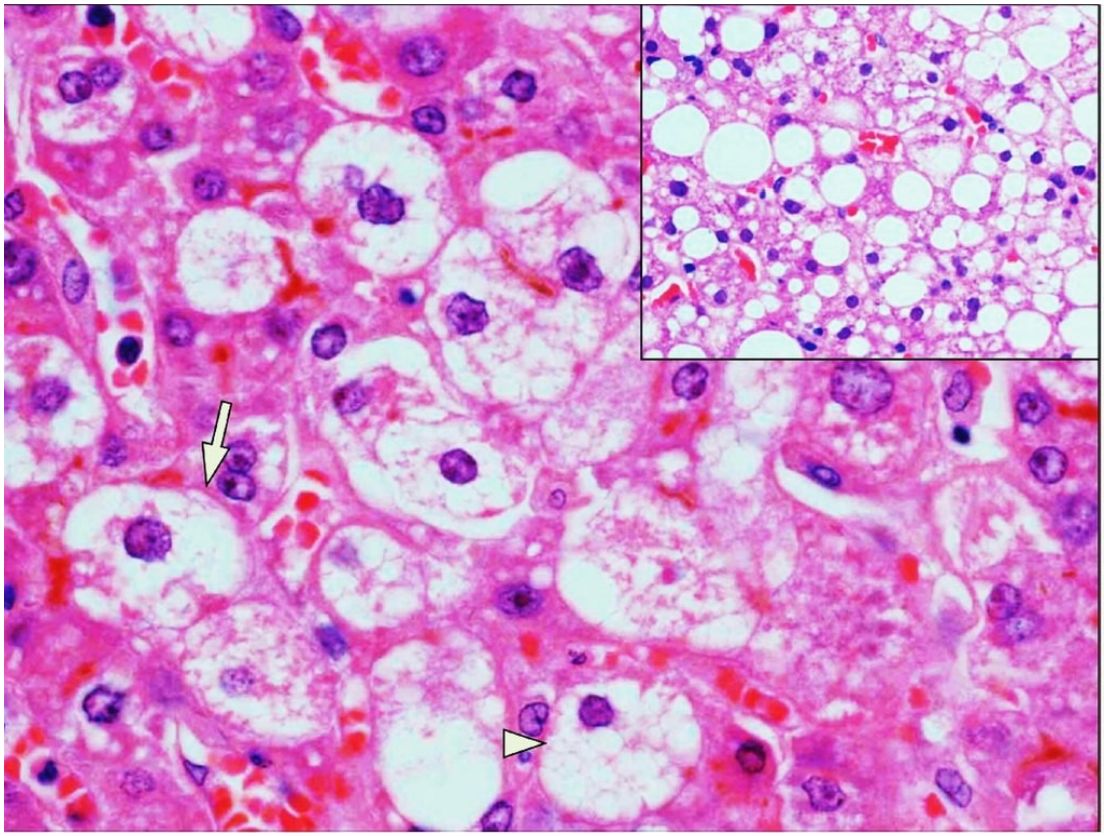

*Figure 2. Histopathology of microvesicular steatosis*

*The central vein and sinusoids appeared dilated and congested, with swollen lipocytes in the space of Disse. Kupffer cells exhibited moderate hypertrophy, with some containing phagocytosed inclusions.*

*In the early stages of AFLP, hepatocytes appeared enlarged and polygonal, with a matte cytoplasm due to microvesicular swelling of ultrastructural organelles (Figure 3). Nuclei were relatively small, round, and occasionally binucleated. The portal tracts exhibited lymphohistiocytic proliferation.*

*In later stages, hepatocytes displayed diffuse swelling and clearing. The sinusoids remained dilated and congested (Figure 4), with focal diapedetic hemorrhages. Hepatocytes continued to swell, and their cytoplasm appeared pale due to extensive lipid accumulation, particularly in the perinuclear zone. Compared to earlier stages, hepatocyte nuclei became more hypochromatic, containing less chromatin. Hepatocytes in the second and third functional zones exhibited microvesicular fatty degeneration, with lipid vacuoles diffusely distributed, giving the cells a foamy appearance. Some hepatocytes exhibited lipid droplets predominantly localized in the perinuclear zone. The nuclei remained round or oval and were centrally positioned, with evenly distributed chromatin.*

*Renal Involvement: The renal tubular epithelium exhibited microvesicular fatty degeneration, particularly in the convoluted tubules. Glomerular lumina appeared dilated, with thickened outer membranes and lymphoid infiltration around the glomeruli. The proximal tubules displayed mild swelling, with intracytoplasmic microvesicular lipid droplets, particularly in the subcapsular region adjacent to nuclei (Figure 5).*

*Cardiac Involvement: The subendocardial myocardial zone exhibited loosening of muscle fibers, with separation of myofibrils due to the presence of lipid inclusions in the sarcoplasm of cardiomyocytes (Figure 6). These lipid inclusions were concentrated beneath the endocardium and within myocardial tissue surrounding blood vessels. Additionally, multiple petechial*

*hemorrhages were observed on the mucosal and serosal surfaces, consistent with disseminated intravascular coagulation (DIC).*

**Conclusion.**

*During the pre-icteric phase of AFLP, clinical symptoms such as weakness, lethargy, nausea, vomiting, abdominal discomfort, and abdominal pain were accompanied by diffuse microvesicular fatty degeneration of hepatocytes. This histopathological change reflects early mitochondrial dysfunction, where impaired β-oxidation of fatty acids leads to intracellular lipid accumulation. At this stage, hepatocytes typically retain their nuclei, and the hepatic architecture remains preserved, although the cytoplasm becomes vacuolated due to numerous tiny lipid droplets that do not displace the nucleus.*

*In the icteric phase of AFLP, the primary pathomorphological changes in the liver included diffuse fatty degeneration, necrobiosis of nuclear structures, pronounced sinusoidal congestion, and focal diapedetic hemorrhages. These findings indicate a progression from reversible metabolic injury to irreversible cellular damage. Necrobiosis of nuclear structures points to hepatocellular death, while sinusoidal congestion reflects circulatory disturbances secondary to hepatocellular swelling and compromised venous outflow. Diapedetic hemorrhages are suggestive of increased vascular fragility and impaired coagulation, which are common in advanced stages of AFLP due to synthetic liver dysfunction.*

*During the icteric phase of AFLP, dystrophic and destructive processes extended to other parenchymal organs, including microvesicular fatty degeneration of the epithelial cells of the renal convoluted tubules and the subendocardial zone of the myocardium. These systemic changes support the concept of AFLP as a mitochondrial cytopathy, wherein multisystemic energy failure leads to widespread lipid infiltration and cellular dysfunction. Renal involvement, particularly in the form of tubular epithelial steatosis, may contribute to acute kidney injury and exacerbate metabolic imbalances, while myocardial lipid accumulation could compromise cardiac contractility and contribute to hemodynamic instability.*

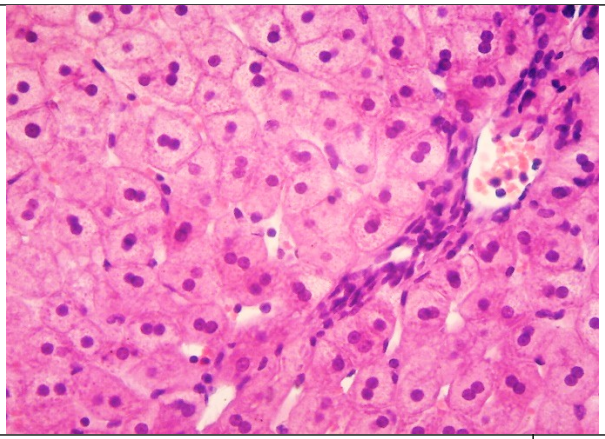

*Figure 3. Pre-icteric phase of AFLP: Cytoplasmic clearing of hepatocytes. Hematoxylin-eosin staining. Magnification: 10×40.*

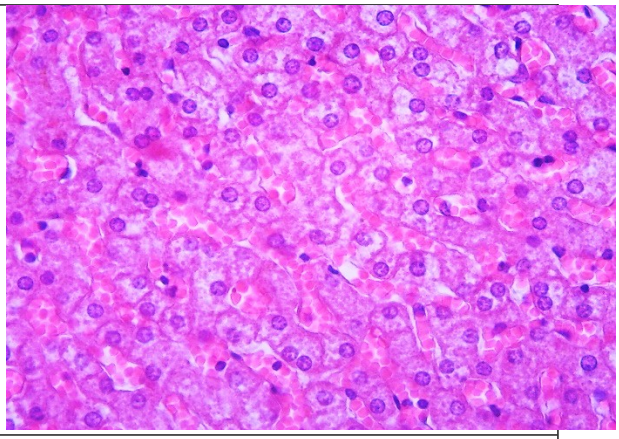

*Figure 4. Icteric phase of AFLP: Diffuse microvesicular fatty degeneration of hepatocytes. Hematoxylin-eosin staining. Magnification: 10×40.*

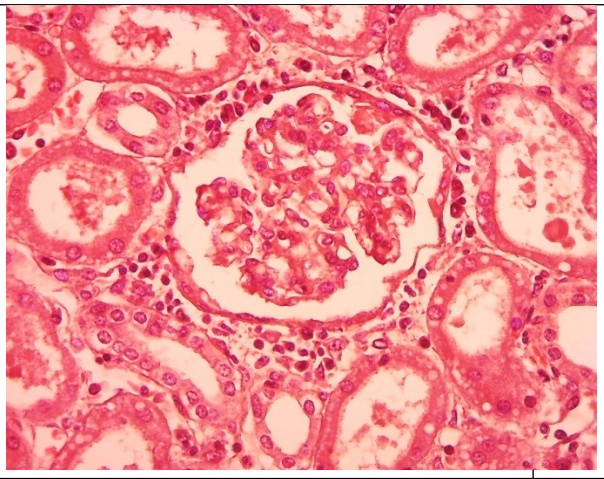

*Figure 5. Microvesicular fatty degeneration of the renal tubular epithelium in AFLP. Hematoxylin-eosin staining. Magnification: 10×40.*

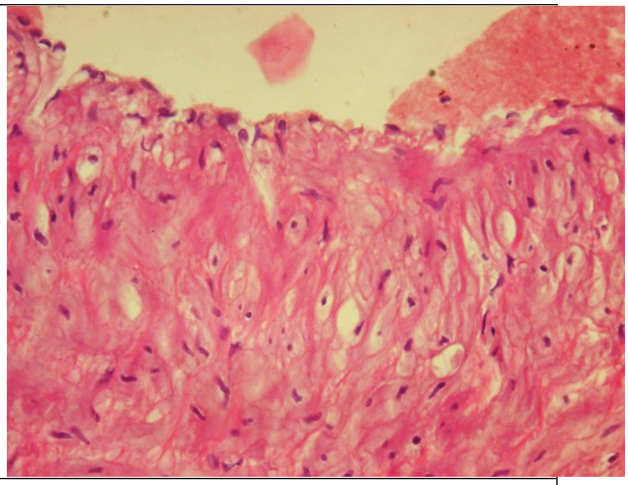

*Figure 6. Fatty degeneration of subendocardial cardiomyocytes in AFLP. Hematoxylin-eosin staining. Magnification: 10×40.*

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