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COMPREHENSIVE REVIEW OF AUTOIMMUNE HEPATITIS: DIAGNOSTIC APPROACHES AND TREATMENT MODALITIES HIGHLIGHTED BY A CASE REPORT

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ABSTRACT: Autoimmune hepatitis (AIH) is a chronic liver disease characterized by immune system dysfunction, elevated gamma globulins, and specific auto antibodies. It arises from genetic predisposition, environmental triggers, and immune dysregulation, and is typically managed with immunosuppressive therapy. The research highlights AIH risks, including disease recurrence and complications from vaccinations like COVID-19 and Hepatitis A, underscoring the need for tailored management and ongoing patient monitoring. We present a rare case of AIH in an adult male with delayed diagnosis. Initially, he experienced jaundice at 14 and managed it with alternative medicine. At 32, he was diagnosed with jaundice, liver dysfunction, and portal hypertension, which progressed despite treatment. By 34, he was diagnosed with decompensated chronic liver disease related to AIH at a government tertiary care hospital. The study explores novel diagnostic approaches, such as neuro-fuzzy cognitive maps, serum biomarkers like GDF15, and gene expression profiling to improve early detection. It also discusses emerging therapeutic strategies, including cytokine modulation and immunoproteasome inhibition, to optimize treatment outcomes. With further research, these methods could save lives, unlike in our patient's case. Despite treatment, the patient's condition worsened, leading to his death in early 2024. This case highlights the importance of timely and accurate diagnosis. Negligence and lack of expertise can result in overlooked diagnoses, causing unnecessary loss of life. This study is dedicated to the patient, emphasizing the need for advancements in AIH care to improve outcomes and quality of life for affected individuals.

INTRODUCTION:

Autoimmune Hepatitis: Autoimmune hepatitis (AIH) is characterized by persistent inflammation of the liver, marked by elevated gamma globulins and tissue-specific autoantibodies. AIH involves chronic and progressive liver inflammation, the exact origin of which remains unknown.

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It is believed to arise from a complex interplay of factors including genetic susceptibility, environmental triggers, and immune system dysfunction. This multifactorial process culminates in continuous inflammation of hepatocytes and subsequent liver fibrosis. The pathogenesis of AIH is attributed to an abnormal autoimmune reaction in genetically predisposed individuals, possibly triggered by molecular mimicry between viral and self-antigens. This condition often responds well to immunosuppressive therapy [1].

Classification: Type I autoimmune hepatitis (AIH), the most common subtype, is identified by

the presence of antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA). It exhibits a bimodal age distribution. Type II AIH is characterized by anti-liver kidney microsomal antibodies (anti-LKM1), with ANA and SMA usually absent. Patients with Type II AIH are more likely to present with acute, severe disease and are typically younger, usually between 2-14 years of age, with peaks at 10–20 and at 45–70 years. In adults, a titer of at least 1:80 is considered positive for these antibodies [1].

Grading and staging AIH involve assessing the extent of liver fibrosis. Widely used systems include the four-tiered classifications by Batts and Ludwig, and Scheuer. The French METAVIR system and the modified Knodell system, while more commonly used in research, can also be applied to AIH. Staging is based on the degree of fibrosis [1]:

- **Stage 1:** Expansion of portal tracts without periportal extension.
- **Stage 2:** Periportal fibrosis.
- **Stage 3:** Bridging fibrosis between portal areas and between portal and central areas.
- **Stage 4:** Cirrhosis.

Incidence: In 33 studies meeting inclusion criteria, the global pooled incidence of autoimmune hepatitis (AIH) was 1.28 cases per 100,000 person-years [2]. A 2019 systematic review of 22 studies reported an incidence of 1.37 cases per 100,000 person-years and a prevalence of 17.44 cases per 100,000 people, with higher rates in women and adults over 65 years old [2, 3]. Incidence and prevalence rates have increased significantly since the early 2000s [2].

Despite approximately 25% of AIH patients being asymptomatic, the disease progresses similarly regardless of symptoms, with a two-fold increase in mortality risk and potential for acute-on-chronic liver failure [2, 4, 5, 6]. Predominantly affecting adult females (71-95%) and girls (60-76%), AIH shows age peaks between 10-30 and 40-60 years, with recent reports indicating a later peak onset, particularly in individuals over 60 years old [7, 8, 9]. A New Zealand study observed a 40% increase in AIH prevalence over nine years, with a bimodal age distribution under 20 and 50-69 years, mirroring European cohorts. The reasons behind rising AIH incidence remain unclear, warranting further investigation into potential environmental triggers and contributing factors [10].

Etiology: Autoimmune hepatitis (AIH) is a complex disease with multifactorial origins. The precise cause remains unknown, but genetic susceptibility and environmental triggers play significant roles in its development.

Genetic Susceptibility: AIH is strongly linked to specific genetic markers, particularly human leukocyte antigens (HLA) such as HLA-DR and HLA-DRB1 alleles. These associations vary by ethnicity, influencing AIH susceptibility and clinical characteristics differently among populations [11]. Specific markers like DRB101, DRB103, DRB104, DRB108, DRB113, and DRB114 have been associated with AIH in Indian and Iranian populations, with the DRB1 gene being the only established genetic risk factor for the disease. Possession of DRB103 or DRB104 is even included in the diagnostic criteria for type I AIH by the International Autoimmune Hepatitis Group [12].

AIH shares some clinical features with systemic lupus erythematosus (SLE), suggesting common susceptibility genes between the two diseases. Indeed, genes such as HLA, STAT4, TNIP1, TNFAIP3, and PTPN22 have been identified in both SLE and AIH, highlighting a genetic overlap that underscores the autoimmune nature of these conditions [12]. Additionally, the CTLA-4 +49 A/G polymorphism contributes to AIH susceptibility, although its impact is less significant compared to HLA variants [11].

Environmental Triggers: Environmental factors, including drugs and infections, can trigger AIH in genetically predisposed individuals. These triggers may alter hepatocyte epitopes, leading to an immune response through a mechanism known as molecular mimicry, where pathogen antigens resemble liver autoantigens. Certain medications, such as nitrofurantoin and minocycline, are well-documented culprits of drug-induced AIH. More recently, tumor necrosis factor-alpha inhibitors have also been linked to the development of AIH [11].

Immune Pathogenesis: AIH is characterized by a loss of immune tolerance to hepatocyte antigens, leading to liver cell damage mediated by autoreactive T cells. The molecular mimicry hypothesis suggests that pathogens, drugs, and toxins can induce an autoimmune response by mimicking liver antigens. Research involving animal models has shown that viral infections can break immune tolerance, further supporting this hypothesis [11]. Approximately 60% of AIH patients have chronic hepatitis without serologic evidence of a viral infection, and the disease is often associated with the presence of anti-smooth muscle autoantibodies [11]. The pathogenesis of AIH involves T-cell-mediated inflammation, which is triggered by various environmental factors in genetically predisposed individuals. This inflammation leads to continuous liver cell damage and subsequent fibrosis [11].

Pathophysiology: Autoimmune hepatitis (AIH) is a disease characterized by a loss of tolerance to the liver tissue, leading to a self-perpetuating inflammatory process [1].

Its etiology remains unknown, but it is believed to result from a combination of genetic predisposition and environmental triggers [1, 13]. Research suggests that AIH arises from a failure of immune tolerance, particularly in genetically susceptible individuals [13].

Environmental factors, including drugs, chemicals, and infections, are suspected to trigger the autoimmune process [1]. Common triggers for AIH include infections, medications, and toxins [13].

Certain human leukocyte antigen (HLA) haplotypes increase susceptibility to AIH, with variations across different ethnic groups. For instance, susceptible alleles in White North Americans and Northern Europeans are located on the short arm of chromosome 6 within the DRB-1 region [13]. Medications like nitrofurantoin, minocycline, and tumor necrosis factor-alpha inhibitors have been associated with drug-induced AIH [13]. Interface hepatitis is a hallmark histological feature of AIH [13].

FIG. 1: THE POSSIBLE THEORIES OF ETIOPATHOGENESIS OF AIH [14, 74, 75]

We categorized the factors involved in AIH pathophysiology into five main areas: environmental factors, immunology, genetics, epigenetics, and other factors. Environmental factors include hepatitis viruses, other viral infections, drug-induced liver injury, chemical compounds, and medication effects. In terms of immunology, the chart outlines the roles of innate and adaptive immunity, immune dysregulation, and humoral and cellular immunity. The genetics section highlights genetic syndromes, non-HLA genetic factors, and HLA associations. Epigenetic factors are represented by microRNA and biomarkers, histone methylation, and research needs. Lastly, other factors encompass alcohol, pets, parasites, pregnancy, transplantation, vitamin D deficiency, and microbial infections. This comprehensive chart (in **Fig. 1**) underscores the complexity of AIH, illustrating the interplay between genetic predispositions, immune system abnormalities, environmental triggers, and epigenetic modifications in the pathogenesis of the disease.

Clinical Presentation: In a study, upon initial presentation, acute onset autoimmune hepatitis (AIH) commonly manifests with jaundice (94%), fatigue (44%), pruritus (31%), abdominal pain (29%), fever (12%), hepatomegaly (8.6%), splenomegaly (8.6%), and joint pain (7.1%) [61]. Similarly, another study mentions that symptoms may initially be non-specific, gradually progressing to acute hepatitis with jaundice, dark urine, and pale stools in severe cases. Some patients experience a slow, insidious progression of symptoms over months to years, including malaise, headache, anorexia, weight loss, arthralgia, abdominal pain, and relapsing jaundice. About 10% of patients may present with symptoms of end-stage liver disease, such as digestive bleeding and splenomegaly [14]. In a study involving 70 patients with acute onset AIH, additional symptoms included diabetes mellitus (10%) and thyroid disease (7.1%) [15].

Positive antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and elevated IgG levels were observed in 61%, 69%, and 86% of patients, respectively [15]. Biochemically, all patients exhibited significantly elevated transaminase levels, with 50% having elevated international normalized ratio (INR) values. However, normal total bilirubin (TB) levels were observed in 5% of patients, normal alkaline phosphatase (ALP) levels in 33%, and normal albumin levels in over 40% of patients [15].

Histologically, severe inflammation (Grade 3) was present in 70% of cases, with 38.7% showing advanced fibrosis (Stage 3-4) upon presentation. These findings align with the insidious course of AIH, characterized by phases of exacerbation and remission [15].

Autoimmune Hepatitis: Diagnostic and Clinical Overview:

Asymptomatic Cases: Approximately 20–25% of AIH patients are asymptomatic at diagnosis, often detected through routine liver biochemical testing [62].

Serum Autoantibodies: The three most commonly reported autoantibodies in AIH are antinuclear antibodies (ANA), anti-smooth muscle antibodies (SMA), and anti-liver–kidney microsomal antibodies (LKM) [62].

Scoring Systems: The International Autoimmune Hepatitis Group has developed a scoring system, initially for research purposes, later adopted in clinical practice [1].

Diagnosis: There is no pathognomonic marker for AIH, necessitating exclusion of other liver diseases with similar presentations [7].

Biochemical Findings: AIH typically exhibits a hepatocellular pattern in biochemical profiles, with bilirubin and aminotransferase levels ranging from just above the upper limit of normal (ULN) to >50 times ULN. Elevated gamma-glutamyl transferase (GGT) levels are also common, along with characteristically high IgG levels [7].

Autoantibodies: Diagnosis relies on the presence of specific antibodies: Type 1 AIH is characterized by ANA and/or ASMA/anti-actin antibodies, while Type 2 AIH typically presents with anti-LKM1 antibodies, usually without ANA and ASMA[7].

Histology: Liver biopsy is essential, revealing typical features such as interface hepatitis, plasma cell infiltration, lobular hepatitis, centrilobular

necrosis, emperipolesis, hepatocyte rosettes, cirrhosis, and multilobular or bridging necrosis. AIH features are not unique, necessitating exclusion of other liver diseases [7, 16].

Diagnostic Scoring Systems: The simplified scoring system includes parameters such as autoantibody presence, serum IgG concentration, histological findings, and absence of viral hepatitis markers[7].

Biomarker Panels: Commonly used biomarker panels include FIB-4, FibroTest, enhanced liver fibrosis test, and serum AST/platelet ratio index (APRI) [7, 17].

Other Diagnostic Methods: Advanced imaging techniques like VCTE, MRE, and ARFI help assess liver stiffness and fibrosis for a comprehensive evaluation [7].

Differential Diagnosis: AIH must be differentiated from similar liver diseases like primary biliary cirrhosis, primary sclerosing cholangitis, and viral hepatitis types A, B, C, D and E [13].

Diagnostic Criteria for AIH-PBC Overlap Syndrome (Proposed by Chazouillères *et al.*, 1998):

1) Autoimmune Hepatitis (AIH) (2 out of 3 criteria required) [18]:

- ALT levels >5 times ULN.
- Serum IgG levels >2 times ULN or positive ASMA.
- Liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis [18].

2) Primary Biliary Cholangitis (PBC) (2 out of 3 criteria required) [18]:

- AP levels >2 times ULN or GGT levels >5 times ULN.
- Positive test for antimitochondrial antibodies (AMA).
- Liver biopsy specimen showing florid bile duct lesions [18].

Novel Diagnostic Approaches:

Neuro-Fuzzy Cognitive Maps (AI Model) in Autoimmune Hepatitis Diagnosis: This study introduces a new method called the neuro-fuzzy cognitive map (NFCM), which combines fuzzy cognitive maps (FCM) with neuro-fuzzy inference systems (NFIS). The NFCM method enhances accuracy by using NFIS to determine the causal relationships between concepts, utilizing both expert knowledge and data to calculate the weights of these relationships.

The NFCM model stands out for its high convergence speed and achieved an impressive 89.81% accuracy in diagnosing autoimmune hepatitis (AIH). Unlike traditional FCM, NFCM uses NFIS to determine the strengths of the connections and trains the system's parameters, resulting in better performance [19].

For the best results, the model should have a high true positive rate (TPR) and a low false positive rate (FPR). NFCM surpasses other FCM variations in identifying AIH patients accurately. The NFCM method adjusts the parameters of fuzzy rules by training the system with both expert knowledge and real data. This makes it excellent for dealing with uncertainty, hesitation, or incomplete information.

To evaluate its effectiveness, the NFCM model was tested for AIH detection and compared with RBFCM, iFCM, and FGCM models. The results confirmed that NFCM has superior performance. With its fast convergence and high accuracy, NFCM proves to be an effective and reliable method for AIH diagnosis [19, 20].

Serum GDF15 as a Diagnostic Biomarker for Autoimmune Hepatitis: This study found that serum GDF15 levels are higher in patients with autoimmune hepatitis (AIH), especially those without cirrhosis, compared to other liver diseases. GDF15 was identified as a potential diagnostic marker for AIH through ROC analysis. Immunohistological staining showed GDF15 positivity in liver cells and inflammatory cells in AIH patients, with levels decreasing after treatment remission. The study excluded patients with conditions that elevate GDF15 (e.g., cancer, cardiovascular disease) to clarify its relationship with liver disease. Higher GDF15 levels correlated with liver fibrosis markers and liver damage indicators (TB, AST, PT-INR), and inversely with albumin [21].

Though the AIH sample was small, the significant reduction in serum GDF15 levels post-treatment supports its association with liver inflammation and damage. The study concludes that GDF15 is a useful diagnostic and therapeutic biomarker for AIH, suggesting further research to explore its predictive value for relapse and prognosis [21, 22].

Gene Expression Profiles, Regulatory T Cells, and PD-1 Pathway as Diagnostic Tools in Autoimmune Hepatitis:

Adult AIH: Gene expression profiles, such as IFN-ɣ, T-bet, and IL-22, show higher expression in AIH patients compared to healthy controls. Various cytokines and chemokines are associated with immune activation in AIH, including IL-6, IL-8, IL-21, IL-23, CCL2, CXCL9, and CXCL10. Conversely, immune quiescence is linked to IL-2, IL-4, IL-10, CCL22, CCL13, and eotaxin-1 (CCL11).

Other noteworthy biomarkers include ADA, cytokeratin-18 death marker M65, TGF-ß1, BAFF, Anti-ASGPR, FOXP3/RORɣt ratio, DNAse 1, ferritin, CD74: MIF ratio, and the vitamin D receptor. Regulatory T cells (Tregs) are also promising as protective markers or therapeutic targets in AIH, similar to their role in organ rejection and drug-induced liver injury (DILI) [23, 24].

Pediatric AIH: The PD-1 pathway is significant in pediatric AIH. Children with AIH at diagnosis have higher levels of soluble PD-1 compared to other liver diseases, correlating with liver fibrosis and the Child-Pugh score. Soluble PD-1 levels are also higher in pediatric AIH patients with active disease versus remission.

In Conclusion, for both adults and children with AIH, a variety of biomarkers, including gene expression profiles, cytokines, chemokines, and other specific markers, could enhance the diagnosis and treatment of AIH. Further research is needed to validate their clinical utility [23, 25].

Microbial Dysbiosis and AIH Diagnosis; Veillonella Enrichment and Disease Activity: This study delves into microbial dysbiosis in autoimmune hepatitis (AIH), revealing lower bacterial diversity and altered abundances in 11 genera. Notably, Veillonella enrichment in AIH correlates with disease activity and advanced liver inflammation. The fecal microbiome in AIH exhibits decreased richness and evenness, with increased *Veillonella, Streptococcus, Klebsiella,* and *Lactobacillus,* and decreased other bacteria.

This shift towards more aerotolerant microbes suggests microbial community changes linked to reduced SCFA production. Veillonella is associated with high AST levels and hepatic inflammation via LPS biosynthesis. A model using *Veillonella, Lactobacillus, Oscillospira,* and *Clostridiales* accurately distinguishes AIH from healthy controls, validated in an independent cohort. Additionally, *Veillonella dispar* increases with disease severity, suggesting potential for a non-invasive stool test in AIH diagnosis and stratification [26].

The inferred metagenomes depict dysfunction in amino acid biosynthesis and metabolism pathways, particularly tryptophan and arginine. Altered tryptophan metabolism affects epithelial barrier function, while depleted arginine metabolism contributes to AIH pathology. Furthermore, *Enterococcus gallinarum* can translocate to the liver, triggering an autoimmune response in AIH.

Strengths include sample collection pre-steroid treatment, a large cohort, and detailed AIH phenotyping. However, limitations include medication exclusions and single-center design, urging multicenter studies for generalization. Further research is needed to understand the role of Veillonella dispar in AIH pathogenesis [26, 27].

Evaluating HE4 as a Novel Biomarker for Disease Severity in Autoimmune Hepatitis: This study examines the association between serum HE4 levels and disease severity, as well as hepatic fibrosis in autoimmune hepatitis (AIH). Results show significantly elevated serum HE4 levels in AIH patients with liver cirrhosis (AIH-LC) compared to AIH patients and healthy controls. HE4 levels strongly correlate with the severity of hepatic fibrosis and cirrhosis in AIH, demonstrated by correlations with markers of liver cirrhosis severity.

HE4, a member of the Whey Acidic Proteins family, inhibits the degradation of type I collagen, suggesting its potential role in liver fibrosis. The United States Food and Drug Administration approves HE4 as a biomarker for monitoring

ovarian cancer recurrence and progression. Notably, serum HE4 levels show promise as a potential marker for liver fibrosis, as indicated by their correlation with Child-Pugh class and ascites [28]. In conclusion, elevated serum HE4 levels are associated with AIH-LC and correlate with hepatic fibrosis severity. HE4 shows potential as a novel biomarker for assessing disease severity and hepatic fibrosis in AIH, warranting further exploration of its diagnostic and prognostic utility [28, 29].

Proteomic Biomarkers for Autoimmune Hepatitis (AIH): Insights from Differential Protein Expression: This study identifies 16 proteins with nominally significant differential expression in the circulation of patients with autoimmune hepatitis (AIH). These proteins, including CA1, CA3, GAS6, FCGR2A, and CXCL10, exhibit both up-regulation and down-regulation in AIH patients compared to controls. Notably, GAS6, FCGR2A, CXCL10, and CCL19 are up-regulated, while CA1, CA3, and 4E-BP1 are down-regulated.

While these proteomic profiles do not distinguish between different types of AIH or between AIH and AIH with autoimmune sclerosing cholangitis (AIH-ASC), the identified proteins offer potential as new biomarkers for AIH. GAS6, for instance, promotes hepatic stellate cell activation and may attenuate hepatic fibrosis. FCGR2A, another up-regulated protein, is involved in IgG antibody effects on leukocytes [30].

Although studies have not shown an influence of certain polymorphisms on type 1 AIH, various biomarkers have been identified in adult AIH patients, such as heterogenous nuclear ribonucleoprotein A2/B1 and liver arginase. Additionally, vitamin D deficiency is common in AIH, with vitamin D playing a role in regulating toll-like receptor activation and cytokine production [30].

In summary, this pilot study provides insight into the proteomic profile of pediatric AIH compared to controls, highlighting potential biomarkers for disease diagnosis and management. Further research is needed to validate these findings and elucidate their clinical significance in AIH [30, 31].

Cost-Effective Strategies for AIH Diagnosis: Leveraging Proteomics and Protein Chip Technologies: This study demonstrates the efficacy of proteomics, particularly protein chip technologies, in diagnosing and prognosing autoimmune hepatitis (AIH). Through a two-phase strategy involving initial screening of a high-content human protein chip followed by extensive profiling using an AIH-specific chip, 11 potential autoantigens were identified, with three confirmed as AIH-specific.

The approach yielded high diagnostic accuracy, validated by additional AIH samples in a double-blind format. The newfound autoantigens shed light on anti-nuclear autoantibody composition, enhancing understanding of AIH pathogenesis [32]. This novel strategy showcases the potential of high-throughput protein microarray technology in rapidly discovering vital biomarkers for autoimmune diseases. Its efficiency and cost-effectiveness mark it as a promising tool for advancing AIH diagnosis and potentially improving management of various autoimmune conditions [32, 33].

Non-Invasive Diagnostic Tools: The AIH Nomogram: In a study they developed a nomogram to predict the risk of autoimmune hepatitis (AIH) using four key factors: Age, Fasting Blood Glucose (FBG), Gamma-Glutamyl Transpeptidase (GGP), and Anti-actin Antibodies (AA). External validation confirmed its predictive value, establishing it as a useful clinical tool. Although their study model's sensitivity (68.75%), specificity (76.6%), and accuracy (73.6%) are slightly lower than the 2008 diagnostic standard, it still provides a valuable supplement [34].

Notably, FBG levels are lower in AIH patients compared to healthy individuals, supporting studies that link FBG with liver function through the Wnt/β-catenin signalling pathway. AIH can affect individuals at any age, but the study highlights significant risk peaks around puberty and between 40-60 years. However, the model, which does not include liver biopsy data, faces limitations in identifying drug-induced liver injury. Despite this, the nomogram offers an intuitive, non-invasive method to understand AIH risk factors, enhancing clinical decision-making and patient care [34, 35].

Treatment for Autoimmune Hepatitis:

Pre-Treatment Considerations: Before initiating treatment for autoimmune hepatitis (AIH), several factors need consideration:

Thiopurine Methyltransferase (TPMT): Assessment of TPMT levels is important as it helps predict the risk of thiopurine-induced myelosuppression [7, 36]. Thiopurine methyl-transferase (TPMT) is essential in azathioprine metabolism, producing both active (immunosuppressive) and inactive metabolites. Testing TPMT activity before azathioprine treatment can prevent severe myelosuppression, especially in patients with low TPMT levels. However, TPMT testing is not always reliable in predicting toxicity, as some patients with normal TPMT still experience side effects. Routine TPMT testing is recommended for high-risk groups to improve safety and patient confidence, though its universal application is debated. Measuring 6-thioguanine nucleotide levels directly may offer advantages but shows inconsistent clinical correlations in autoimmune hepatitis [37].

Vaccination: Recombinant and inactivated vaccines are safe for AIH patients. Vaccination against hepatitis A virus (HAV) and hepatitis B virus (HBV) is crucial for those who are not already protected [7, 36].

HBV Reactivation Detection and Prevention: Prophylactic antiviral therapy with drugs like entecavir or tenofovir is recommended during immunosuppressive treatment and for at least six months afterward to prevent HBV reactivation[7, 36].

A review discusses the rising incidence of hepatitis B virus reactivation (HBVr) during immunosuppressive therapy, particularly with the introduction of potent new drugs. Chronic HBV carriers face a higher risk compared to those with resolved or occult HBV infection. The article highlights the lack of consensus on optimal durations for antiviral prophylaxis before and after immunosuppressive therapy. Standardizing definitions and terminology is crucial for accurately assessing HBVr incidence and risks across different clinical contexts. Improved HBV screening protocols before starting immunosuppressive therapy and unified guidelines for managing HBVr are essential, urging collaborative efforts in scientific research [38].

Osteoporosis Management: Patients on glucocorticoid treatment should receive elemental calcium and vitamin D supplementation to prevent osteoporosis [36]. Bisphosphonates and weight-bearing exercises are recommended if osteoporosis is present [7]. Research on denosumab's long-term effects in autoimmune hepatitis (AIH) reveals promise. Denosumab, targeting RANKL, improves bone density and reduces TRACP-5b and ALP3 markers in AIH patients. Cortical bone loss in AIH is primarily age-related, not disease severity-driven. Denosumab shows potential for treating AIH-related osteoporosis, necessitating larger studies [39]. Additionally, another study utilizing HR-pQCT has identified significant cortical bone loss in AIH, attributed to aging rather than disease severity. Unlike other conditions, AIH exhibits predominant cortical over trabecular bone loss, influenced by inflammation, glucocorticoid therapy, and liver fibrosis. HR-pQCT aids in assessing fracture risk and guiding AIH-specific bone treatments [40].

First-Line Treatment: Autoimmune hepatitis (AIH) is effectively managed through a structured treatment approach that begins with the induction phase, where prednisone is administered either alone or in combination with azathioprine. This combination is designed to prevent disease progression and promote the regression of fibrosis and cirrhosis. Prednisone's effectiveness in reducing inflammation and inducing remission has been well-documented in clinical trials from the 1970s [41], which demonstrated a significant reduction in mortality rates compared to placebo and azathioprine monotherapy. By combining azathioprine with prednisone, the required dose of steroids can be reduced, thereby minimizing steroid-related side effects such as cushingoid features, osteoporosis, and diabetes. Azathioprine, although not effective alone for inducing remission, plays a crucial role in maintenance therapy due to its immunosuppressive properties, which primarily involve the suppression of nucleic acid synthesis. For patients who are intolerant to azathioprine, mycophenolate mofetil (MMF) can be used as an alternative.

This combination strategy of prednisone and azathioprine not only optimizes disease control but also mitigates the adverse effects associated with high-dose steroid use, providing a balanced and effective treatment regimen for AIH [7, 36, 42].

Maintenance: After achieving biochemical remission, patients should undergo regular laboratory testing. Steroid withdrawal can be attempted while continuing azathioprine[7, 36].

Second-Line Treatment: When initial treatments fail to adequately manage autoimmune hepatitis (AIH), alternative therapeutic approaches become necessary. Azathioprine, a standard first-line treatment, may provoke side effects or fail to achieve sufficient disease control in some patients. In such cases, alternative medications like mycophenolate mofetil (MMF) or calcineurin inhibitors such as cyclosporine A and tacrolimus are considered. MMF serves as a second-line option for patients intolerant to azathioprine, although its use is limited by cost and concerns over teratogenicity. Calcineurin inhibitors, while effective for refractory AIH cases, are associated with significant side effects. For instance, cyclosporine A and tacrolimus require careful monitoring due to their potential for nephrotoxicity and other adverse reactions.

In contrast, mTOR inhibitors like sirolimus and everolimus have shown promise but require further investigation to determine their efficacy and safety profiles in AIH management. These alternative therapies aim to provide effective disease control while mitigating the adverse effects associated with high-dose steroid regimens, particularly in patients where conventional treatments have proven insufficient or intolerable [7, 36, 42].

Liver Transplantation: Liver transplantation may be necessary for patients with AIH who develop acute liver failure or end-stage liver disease [7, 36].

Future Biologic Therapy: Biological agents like rituximab and infliximab are emerging options for treating autoimmune hepatitis (AIH), particularly in refractory cases. Rituximab, specifically, shows promise by depleting B cells and modulating T-cell responses, which are pivotal in AIH autoimmunity. However, these biologics carry risks of serious side effects.

For azathioprine-intolerant patients, alternatives such as thiopurines like 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG) offer another avenue but pose potential long-term safety issues. Allopurinol is being explored for managing skewed thiopurine metabolism but requires further study [7, 36, 42].

Novel Therapeutics Approaches:

Cost-Effectiveness and Affordability of Methotrexate (MTX) in AIH Treatment: Methotrexate (MTX) is endorsed as a second-line therapy for autoimmune hepatitis (AIH) by major liver disease associations, although evidence supporting its efficacy is primarily derived from just four case reports, two of which involve paediatric patients. These reports indicate a notable reduction in prednisolone dosage among MTX responders compared to non-responders. However, a considerable proportion of individuals discontinued MTX within 12 months due to deteriorating liver biochemistry, with some experiencing suspected drug-induced liver injury (DILI). Notably, older patients seemed more likely to respond to MTX treatment [43].

Despite these limitations, MTX remains attractive due to its affordability, wide availability, and weekly dosing regimen, potentially enhancing patient adherence. Given the limited treatment options for AIH refractory to standard therapies, MTX holds promise for patients intolerant or unresponsive to first-line treatments. However, further prospective trials are necessary to establish MTX's efficacy and identify predictors of response in AIH management [43, 44].

Efficacy, Safety and Cost Considerations in Choosing between Mycophenolate Mofetil (MMF) and Azathioprine for AIH Therapy: This study highlights the practical implications of using mycophenolate mofetil (MMF) as part of the standard treatment for treatment-naive autoimmune hepatitis (AIH) patients. MMF, despite its improved efficacy and lower adverse event rate compared to azathioprine, poses high teratogenicity risks, making it unsuitable for pregnant individuals. Azathioprine, in contrast, is considered safe during pregnancy. Considering these factors, a two-tier treatment algorithm may be beneficial for fertile-aged patients, favouring azathioprine unless active pregnancy is desired [45].

Notably, MMF requires twice-daily dosing, while azathioprine is administered once daily. The study found no serious adverse events with MMF, unlike azathioprine, supporting MMF's superior tolerability in AIH management. However, further research is needed to assess MMF's long-term efficacy and its role in sustaining biochemical remission. These findings could inform international guidelines on AIH treatment, while future research should explore novel immunomodulatory agents to enhance treatment strategies [45, 46].

Mesenchymal Stem Cells (MSCs) as Promising Therapeutic Agents in Autoimmune Hepatitis (AIH): Translating Animal Research to Clinical Practice: Recent research has demonstrated the therapeutic potential of mesenchymal stem cells (MSCs) in animal models of autoimmune hepatitis (AIH). MSC administration has shown to alleviate experimental autoimmune hepatitis (EAH) by upregulating PD-L1, inhibiting IL-17, and preventing hepatocyte apoptosis. Genetically modified MSCs with IL-35 have increased efficacy in AIH treatment by reducing FasL expression and suppressing IFN-γ through specific signalling pathways [47]. Additionally, MSC-derived exosomes have exhibited promising therapeutic effects by inhibiting inflammatory cytokines. In a clinical case, a patient diagnosed with AIH type I underwent hematopoietic stem cell transplantation (HSCT) after conditioning. Despite the success of MSC therapy in animal studies, clinical trials investigating its efficacy in AIH treatment are lacking. Further basic and clinical research is essential to validate the therapeutic potential of MSCs in AIH and explore potential synergies with other immunomodulatory compounds. Additionally, MSCs may play a role in supporting HSCT and preventing graft failure, warranting further investigation [47, 48].

Emotional Impact of Fertility Preservation on Autoimmune Hepatitis (AIH) Patients: Providing Hope and Coping Support: Fertility preservation is essential for patients undergoing treatments that could harm reproductive health, including those with Autoimmune Hepatitis (AIH). For young women with AIH, particularly those needing immunosuppressive therapy or liver transplantation, fertility preservation options like embryo, ovarian tissue, and oocyte cryopreservation should be considered. Embryo cryopreservation, the only established method, may not be feasible for all due to the need for a male partner. Ovarian tissue cryopreservation offers estrogen activity post-transplantation but requires two surgeries and has limited graft survival time. Oocyte cryopreservation, initially studied in mice, has been adapted for humans with varying success rates. The newer vitrification method, involving ultra-rapid cooling, shows higher effectiveness compared to slow freezing [49].

For AIH patients needing urgent or unsafe gonadotropin ovarian stimulation, in vitro maturation (IVM) of immature oocytes, followed by fertilization or vitrification, is a safe alternative. These fertility preservation methods provide emotional relief to AIH patients by offering the hope of future biological children, helping them cope better with their treatment journey [49, 50].

Clinical Trials and Therapeutic Implications:
Cytokine Modulation Approaches: Novel Methods for Balancing IL-6 and IL-17 Levels in AIH Management: Elevated IL-6 levels in autoimmune hepatitis (AIH) contribute to inflammation and immune dysregulation [51], while IL-17 exacerbates liver inflammation by stimulating IL-6 production. Patients with AIH often exhibit impaired regulatory T cell (Treg) function, crucial for immune balance. However, Treg function may improve during remission. Treg cells from AIH patients are less effective suppressors and have more IL-17-producing cells. Targeting IL-17 or Th17 differentiation may stabilize Treg cells, offering a promising therapeutic avenue for AIH. Understanding these cytokine interactions could reveal crucial disease mechanisms and treatment targets [52].

Immunoproteasome Inhibition: Exploring Zetomipzomib's Mechanism of Action in Autoimmune Hepatitis Therapy: Kezar Life Sciences is running a Phase 2a trial (PORTOLA) to test zetomipzomib in adults with autoimmune hepatitis who did not respond to standard corticosteroid treatment [53, 55]. Zetomipzomib aims to suppress the immunoproteasome, potentially reducing autoimmune attacks. The trial will measure safety, effectiveness, and remission rates.

Kezar is also investigating (PALIZADE) Phase 2b clinical trial, investigating zetomipzomib's potential in treating lupus nephritis [56]. Initial results showed safety and some patients entering remission [54].

Necroptosis Modulation: Exploring zVAD's Potential as a Therapeutic Agent for Autoimmune Hepatitis: Autoimmune hepatitis (AIH) is on the rise, with limited treatment options available. Recent research led by Prof. DIAO Hongyan from Zhejiang University School of Medicine reveals that zVAD, a compound, can alleviate AIH in mice by enhancing macrophage necroptosis sensitivity through IL-10-induced TNFR1 expression. This study suggests a promising avenue for AIH treatment by targeting macrophage necroptosis [57]. Sibiriline (Sib), identified as a potential therapy for autoimmune hepatitis (AIH), inhibits TNF-induced necroptosis in FADD-deficient cells by competitively binding to the ATP-binding site of RIPK1, thereby blocking RIPK1-dependent necroptosis and apoptosis without affecting caspase-dependent apoptosis. This mechanism protects against liver inflammation and damage in mouse models of concanavalin A-induced hepatitis, indicating Sib's promise as a targeted treatment for AIH [58].

The MERLIN Trial: Exploring a Novel Approach to Treating Primary Sclerosing Cholangitis and Autoimmune Hepatitis: The MERLIN trial, led by the University of Birmingham, is investigating a new cellular immunotherapy for treating Primary Sclerosing Cholangitis (PSC) and Autoimmune Hepatitis (AIH). It involves 56 patients receiving a single infusion of specially selected mesenchymal stromal cells (MSCs), with the first patient already treated at Queen Elizabeth Hospital Birmingham. Sponsored by the University of Birmingham and coordinated by the Cancer Research UK Clinical Trials Unit, the trial aims to prove the safety and efficacy of the treatment. ORBCEL-C™, the cell product used, was discovered by Dr. Steve Elliman from Orbsen Therapeutics, and is manufactured by NHS Blood and Transplant in Birmingham[59, 60].

Risks related to AIH:

Recurrent AIH Risk: A study led by Aldo Montano-Loza, MD, PhD, from the University of Alberta in Canada, examined risk factors for recurrent autoimmune hepatitis (AIH) after liver transplantation. Analyzing data from 736 AIH patients across 33 international centers, the study identified several factors associated with higher recurrence rates, including younger age at transplantation, use of mycophenolate mofetil post-transplantation, sex mismatch between donor and recipient, and elevated IgG levels before transplantation. Recurrent AIH was also linked to increased risk of graft loss and mortality. These findings underscore the importance of recognizing and managing risk factors to improve outcomes in AIH patients post-transplantation [61].

Vaccination Risks in AIH:

COVID-19 Vaccination: A recent study published in the Journal of Hepatology highlighted a case of immune-mediated hepatitis following COVID-19 vaccination. The patient, a 52-year-old male, developed symptoms after receiving the first and second doses of the BNT162b2 vaccine. Laboratory tests and liver biopsy suggested acute mixed hepatitis, resembling autoimmune hepatitis (AIH). Treatment with budesonide resulted in symptom improvement, but relapses occurred. Analysis revealed an abundance of cytotoxic CD8 T cells in the liver, implicating T cell-mediated immune response triggered by the vaccine. These findings suggest a potential association between COVID-19 vaccination and immune-mediated hepatitis, emphasizing the need for further research and vigilance in monitoring vaccine-related adverse events [62, 63].

Similarly, in another study, Cases of autoimmune hepatitis (AIH) following COVID-19 vaccination have been increasingly reported, involving around 27 instances. These cases include patients with backgrounds like primary sclerosing cholangitis, liver transplantation, and prior hepatitis C virus treatment. Potential mechanisms implicated include molecular mimicry, adjuvants, epitope spreading, bystander activation, X chromosome involvement, and possible SARS-CoV-2 hepatotropism. Treatment typically involves immunosuppressive corticosteroids, sometimes combined with azathioprine, showing effectiveness in managing AIH post-vaccination. However, further investigation is necessary to establish causality and fully comprehend the underlying mechanisms [64].

Hepatitis A Vaccine: In a case study, they discussed a potential link between vaccination and autoimmune hepatitis (AIH), particularly following immunization with the hepatitis A vaccine (HAV). Although the vaccine's safety profile traditionally does not include recrudescence of hepatitis or autoimmune reactions, this patient's experience suggests otherwise. Vaccination with inactivated HAV has been considered safe since its introduction, and there have been no reports of adverse reactions in individuals with pre-existing liver conditions. However, autoimmune responses triggered by viral antigens in susceptible individuals, possibly through mechanisms like molecular mimicry, remain a subject of investigation. The emergence of AIH symptoms post-vaccination, despite the vaccine's inactivation process, raises intriguing questions about potential immune reactions directed at liver antigens. Further research is crucial to elucidate these mechanisms and determine the actual risk-benefit balance of vaccination in individuals predisposed to autoimmune liver disorders [65].

Case Study on Autoimmune Hepatitis: We present a rare case of Autoimmune hepatitis in an adult male with a delayed diagnosis. The patient experienced jaundice at the age of 14, which resolved after using complementary and alternative medicines (CAM).

Clinical Status of the Patient in 2021: At the age of 32, nearly 20 years after his initial diagnosis, he was once again diagnosed with jaundice during a visit to a private primary care hospital (1st hospital). Initial examinations indicated liver dysfunction and the development of portal hypertension.

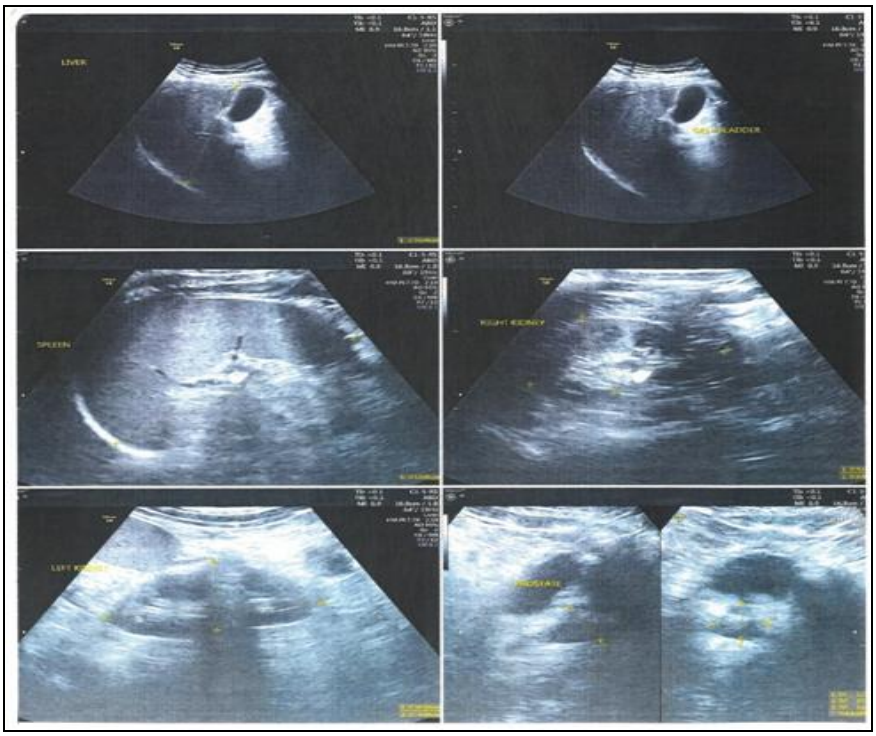

FIG. 2: ABDOMEN AND KUB SCAN REPORT:- REAL-TIME B-MODE ULTRASONOGRAPHY OF ABDOMEN AND KUB: ABDOMEN: LIVER - SIZE: 10.9 cm (NORMAL); ECHOTEXTURE: MILDLY ALTERED COARSE; SURFACE: IRREGULAR; PORTAL VEIN: NORMAL HEPATOPETAL FLOW; FOCAL LESION: NONE SEEN. GALL BLADDER: APPEARANCE: NORMAL; CALCULI: NONE SEEN. COMMON BILE DUCT: APPEARANCE: NORMAL; CALCULI: NONE SEEN. PANCREAS: APPEARANCE: NORMAL. SPLEEN: SIZE: MILDLY ENLARGED, MEASURING 13.1 cm. PERITONEAL CAVITY: APPEARANCE: NORMAL; KIDNEYS, URETERS, AND BLADDER (KUB). RIGHT KIDNEY: SIZE: 9.3 X 4.9 cm (NORMAL SIZE: APPROXIMATELY 10-12 cm IN LENGTH); CORTEX AND COLLECTING SYSTEM: NORMAL; CALCULI: NONE SEEN. LEFT KIDNEY: SIZE: 10.2 X 4.4 cm (NORMAL SIZE: APPROXIMATELY 10-12 cm IN LENGTH); CORTEX AND COLLECTING SYSTEM: NORMAL; CALCULI: NONE SEEN. CORTICAL ECHOES OF BOTH KIDNEYS: APPEARANCE: NORMAL. BLADDER: APPEARANCE: NORMAL. PROSTATE: SIZE: 2.6 X 2.5 X 2.3 cm (WEIGHT: 7.77 g); APPEARANCE: NORMAL; INTRA VESICAL ENLARGEMENT: NONE SEEN. IMPRESSION: COARSE LIVER ECHOTEXTURE: SUGGESTED TO CORRELATE WITH LIVER FUNCTION TESTS (LFT), MILD SPLENOMEGALY.

TABLE 1: THE LABORATORY FINDINGS FOR THE PERIOD OF 2021

Year	Month	Laboratory findings										
		Liver Function Test								Urine Analysis		
		Bilirubin			SGOT	SGPT	S. A. P	GGT	Bile salt	Bile pigment	Albumin	Globulin
		Total	Direct	Indirect								
2021	June	1.87 mg/dl	1.16 mg/dl	0.71 mg/dl	84.6 U/L	59.8 U/L	215.2 IU/L	190.8 U/L	Nil	Negative	Nil	Nil
	July	1.63 mg/dl	1.05 mg/dl	0.58 mg/dl	74.8 U/L	48.2 U/L	224.4 IU/L	191.1 U/L	Nil	Negative	Nil	Nil
	September	1.6 mg/dl	1.13 mg/dl	0.56 mg/dl	73 U/L	49 U/L	219.7 IU/L	192 U/L	Nil	Trace	Nil	Nil
	November	1.48 mg/dl	1.18 mg/dl	0.3 mg/dl	79.1 U/L	44.1 U/L	210.5 IU/L	223.0 U/L	Present	Positive	Nil	Nil

SGOT - Serum Glutamic-Oxaloacetic Transaminase; SGPT- Serum Glutamate Pyruvate Transaminase; S.A.P - Serum Alkaline Phosphatase; GGT- Gamma-Glutamyl Transferase.

An abdominal and KUB scan (in **Fig. 2**) indicated mild coarse echotexture of the liver and an irregular surface, prompting further evaluation through Liver Function Tests (LFT). The average LFT results of 2021 period showed abnormalities (**Table 1**), including significantly elevated direct bilirubin levels of 1.64 mg/dL (normal range: 0 - 0.3 mg/dL), indicative of impaired bilirubin metabolism and excretion. Elevated levels of SGOT (AST) at 77.8 U/L (normal range: 10 - 40 U/L) suggested hepatocellular injury and normal SGPT (ALT) at 50.27 U/L (normal range: 7 - 56 U/L). HBsAg tested negative ruling out hepatitis viral infection.

Further imaging revealed mild splenomegaly, while other organs such as the gall bladder, common bile duct, pancreas, kidneys, bladder, and prostate appeared normal without any calculi or abnormalities. These findings collectively pointed towards significant liver impairment and jaundice, raising concerns about the underlying cause, and necessitating urgent medical evaluation.

Following the diagnosis, treatment included Cap. Essentiale 100 and Udiliv 150mg. The patient's management plan involved regular monitoring of liver function and imaging studies to assess the response to treatment.

Clinical Status of the Patient in 2022: At the age of 33, despite ongoing symptoms, the patient's laboratory findings (**Table 2**) showed an increase in abnormal values compared to the previous year, indicating that the medications were not effective. Consequently, the patient sought care at a private tertiary hospital (2nd hospital) in their local area.

The abdomen and KUB scan revealed parenchymal liver disease characterized by altered coarse echoes and a blunted liver margin. Additionally, the spleen was slightly enlarged, and the pancreas was not clearly visible. The overall impression from the scan confirmed the presence of parenchymal liver disease and splenomegaly, underscoring the progression of the condition over the past year.

TABLE 2: THE LABORATORY FINDINGS FOR THE PERIOD OF 2022

Year	Month	Laboratory findings										
		Liver Function Test								Urine Analysis		
		Bilirubin			SGOT	SGPT	S. A. P	GGT	Bile salt	Bile pigment	Albumin	Globulin
		Total	Direct	Indirect								
2022	Jan	4.1 mg/dl	1.9 mg/dl	2.5 mg/dl	118 U/L	96 U/L	210.4 IU/L	65.1 U/L	Present	Positive	Nil	Nil
	June	4.8 mg/dl	2.1 mg/dl	2.7 mg/dl	116 U/L	97 U/L	210 IU/L	63 U/L	Present	Positive	Nil	Nil
	July	4.1 mg/dl	2.0 mg/dl	2.7 mg/dl	98 U/L	88 U/L	161 IU/L	71.4 U/L	Present	Positive	Nil	Nil
	Sep	2.9 mg/dl	1.7 mg/dl	2.6 mg/dl	48 U/L	45 U/L	153.7 IU/L	61.5 U/L	Present	Positive	Nil	Nil

SGOT - Serum Glutamic-Oxaloacetic Transaminase; SGPT- Serum Glutamate Pyruvate Transaminase; S.A.P - Serum Alkaline Phosphatase; GGT- Gamma-Glutamyl Transferase.

From these findings, it is evident that the 2nd hospital did not accurately diagnose the underlying cause of the disease. Consequently, the previous medications were continued, and additional medications were prescribed, including T. Heptagon 1mg, T. Nusam 200mg, Himalaya LIV 52 DS, and T. Silyban 70mg.

Clinical Status of the Patient in 2023: At the age of 34, he sought consultation at a government tertiary care hospital (3rd hospital). Despite continued medication, the patient's laboratory findings (**Table 3**) showed progressive deterioration. He presented with increasing abdominal distension, a one-month history of bilateral lower limb swelling, yellow discoloration of the eyes and urine, and bleeding per rectum. He denied any history of hematemesis, melena, altered sleep patterns, altered sensorium, clay-colored stools, or decreased urine output. Additionally, he had no known history of type 2 diabetes mellitus, tuberculosis, epilepsy, asthma, seizure disorders, or alcohol use.

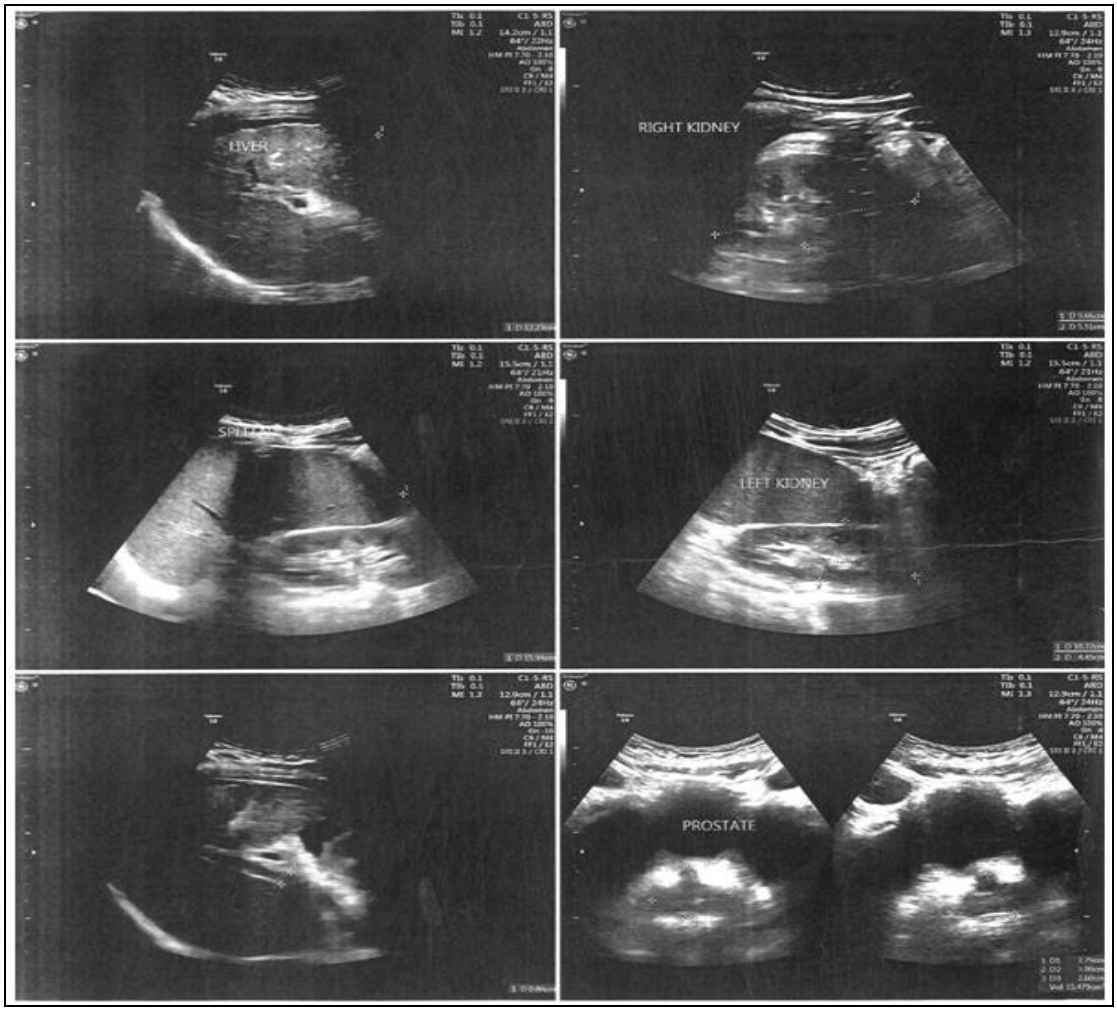

FIG. 3: ABDOMEN AND KUB SCAN REPORT: REAL-TIME B-MODE ULTRASONOGRAPHY OF ABDOMEN AND KUB: ABDOMEN: LIVER- SIZE: 12.3 CM (NORMAL) ; ECHOTEXTURE: MILDLY ALTERED COARSE; SURFACE: IRREGULAR WITH LEFT LOBE HYPERTROPHY; PORTAL VEIN: MEASURES 8 MM AT THE LEVEL OF PORTA HEPATIS; PORTAL VEIN VELOCITY: 19 CM/S, NO PORTAL COLLATERALS; FOCAL LESION: NONE SEEN; GALL BLADDER: APPEARANCE: NORMAL; CALCULI: NONE SEEN; COMMON BILE DUCT: APPEARANCE: NORMAL; CALCULI: NONE SEEN; PANCREAS: APPEARANCE: NORMAL; SPLEEN: SIZE: MODERATELY ENLARGED, MEASURING 15.9 CM; MINIMAL ASCITES NOTED; KIDNEYS, URETERS, AND BLADDER (KUB): RIGHT KIDNEY - SIZE: 9.6 X 5.5 CM; CORTEX AND COLLECTING SYSTEM: NORMAL; CALCULI: NONE SEEN; LEFT KIDNEY: SIZE: 10.3 X 4.4 CM; CORTEX AND COLLECTING SYSTEM: NORMAL; CALCULI: NONE SEEN; CORTICAL ECHOES OF BOTH KIDNEYS: APPEARANCE: NORMAL; BLADDER: APPEARANCE: NORMAL; PROSTATE: SIZE: 3.8 X 3.0 X 2.6 CM (WEIGHT: 15.41 G); APPEARANCE: NORMAL; INTRA VESICAL ENLARGEMENT: NONE SEEN; IMPRESSION: CHRONIC PARENCHYMAL LIVER DISEASE; MODERATE SPLENOMEGALY; MINIMAL ASCITES

TABLE 3: THE LABORATORY FINDINGS FOR THE PERIOD OF 2023

Year	Month	Laboratory findings										
		Liver Function Test							Urine Analysis			
		Bilirubin			SGOT	SGPT	S. A. P	GGT	Bile salt	Bile pigment	Albumin	Globulin
		Total	Direct	Indirect								
2023	January	3.9 mg/dl	1.4 mg/dl	2.5 mg/dl	95 U/L	87 U/L	115 IU/L	79 U/L	Present	Positive	Nil	Nil
	February	3.7 mg/dl	1.0 mg/dl	2.7 mg/dl	87 U/L	71 U/L	152 IU/L	75 U/L	Present	Positive	Nil	Nil
	April	2.12 mg/dl	1.83 mg/dl	2.5 mg/dl	128.9 U/L	47 U/L	216 IU/L	71 U/L	Present	Positive	Nil	Nil
	April	3.1 mg/dl	1.3 mg/dl	2.41 mg/dl	136 U/L	40 U/L	256 IU/L	71 U/L	Present	Positive	Nil	Nil
	May	4.7 mg/dl	2.3 mg/dl	2.74 mg/dl	175 U/L	59 U/L	153 IU/L	74 U/L	Present	Positive	Nil	Nil
	June	5.8 mg/dl	2.8 mg/dl	2.8 mg/dl	92 U/L	36 U/L	179 IU/L	75 U/L	Present	Positive	Nil	Nil
	June	4.7 mg/dl	2.3 mg/dl	2.7 mg/dl	175 U/L	59 U/L	166 IU/L	73 U/L	Present	Positive	Nil	Nil
	July	7.3 mg/dl	4.4 mg/dl	2.78 mg/dl	95 U/L	65 U/L	151 IU/L	78 U/L	Present	Positive	Nil	Nil
	August	5.4 mg/dl	3.2 mg/dl	2.67 mg/dl	59 U/L	39 U/L	145 IU/L	76 U/L	Present	Positive	Nil	Nil
	September	5.5 mg/dl	3.0 mg/dl	2.5 mg/dl	74 U/L	58 U/L	153 IU/L	76 U/L	Present	Positive	Nil	Nil
	November	9.9 mg/dl	6.0 mg/dl	2.9 mg/dl	90 U/L	48 U/L	169 IU/L	77 U/L	Present	Positive	Nil	Nil
	December	7.4 mg/dl	3.7 mg/dl	2.83 mg/dl	92 U/L	66 U/L	158 IU/L	78 U/L	Present	Positive	Nil	Nil

SGOT - Serum Glutamic-Oxaloacetic Transaminase; SGPT- Serum Glutamate Pyruvate Transaminase; S.A.P - Serum Alkaline Phosphatase; GGT- Gamma-Glutamyl Transferase.

Reviewing the progression of his condition, in 2022, scans indicated parenchymal liver disease characterized by coarse echoes and a blunted liver margin, alongside a slightly enlarged spleen. In early 2023 (in **Fig. 3**), subsequent scans showed a normal-sized liver with mildly coarse echotexture, an irregular surface, left lobe hypertrophy, moderate splenomegaly (15.9 cm), and minimal ascites. Later in 2023, the CECT abdomen scan detailed a liver measuring 7.5 cm with irregular surface nodularity and blunted margins, along with caudate lobe hypertrophy. There are a few dilated tortuous splenic hilar and splenorenal collaterals, as well as moderate free fluid in the peritoneal cavity. Enlarged sub centimetric mesenteric and paraaortic lymph nodes are noted. The spleen is enlarged with a splenic index of 638, and hyperdense sludge is present in the gall bladder this progression confirmed chronic parenchymal liver disease and moderate ascites. Further tests, including immunoserological assessments (**Table 4**), were conducted. The Anti Soluble Liver Antigen (SLA) was measured at 1.30 U/mL, which is within the typical reference range of <12.00, indicating a normal result. Immunoglobulin IgG level is elevated at 2275.00 mg/dL, with the normal range generally being 700-1600 mg/dL, suggesting hypergammaglobulinemia, which can be associated with chronic liver disease or autoimmune conditions. The Anti-Nuclear Antibody (ANA) test, which screens for autoimmune disorders, returned a positive result with a nuclear and nucleolar pattern (AC-8,9,10) at a dilution of 1:100, indicating a possible autoimmune pathology (in **Fig. 4**).

This result should be clinically correlated with other laboratory values [68]. The Mitochondrial Antibody (AMA) test was negative at a dilution of 1:40, which is within the normal limits and typically indicates the absence of primary biliary cirrhosis. The Smooth Muscle Antibody (ASMA) test showed a weak positive result at a dilution of 1:40, potentially pointing towards autoimmune hepatitis, though low titers can be seen in other conditions. Lastly, the Liver Kidney Microsomal (LKM) antibody test was negative at a dilution of 1:40, which is generally within normal limits and indicates the absence of autoimmune hepatitis type

2. These results, especially the positive ANA and elevated IgG, along with other laboratory values, suggest the potential for autoimmune liver disease [66, 67].

TABLE 4: IMMUNOSEROLOGICAL ASSESSMENTS

Test Name	Results
Anti Soluble Liver Antigen (SLA), Serum (EIA)	
Anti Soluble Liver Antigen (SLA)	1.30 U/mL
Immunoglobulin IgG, Serum (Immunoturbidimetry)	
Immunoglobulin IgG	2275.00 mg/dL
Anti Nuclear Antibody / Factor (ANA/ANF) IFA (HEP-2) END Point Titre, IFA	
ANA HEp-2	Positive
Pattern	Nuclear, Nucleolar (AC-8,9,10)
Intensity	1+
Primary Titre/Dilution	1:100
End Point Titre/Dilution	1:100
Mitochondrial Antibody (AMA), IFA	
AMA	Negative
Titre	01:40
Smooth Muscle Antibody (ASMA), IFA	
ASMA	Weak Positive
Titre	01:40
Liver Kidney Microsomal (LKM) Antibody In Dilutions, IFA	
LKM Antibody	Negative
Titre	01:40

EIA - Enzyme Immunoassay; Hep-2 - Human Epithelial Cells; IFA - Immunofluorescence Assay

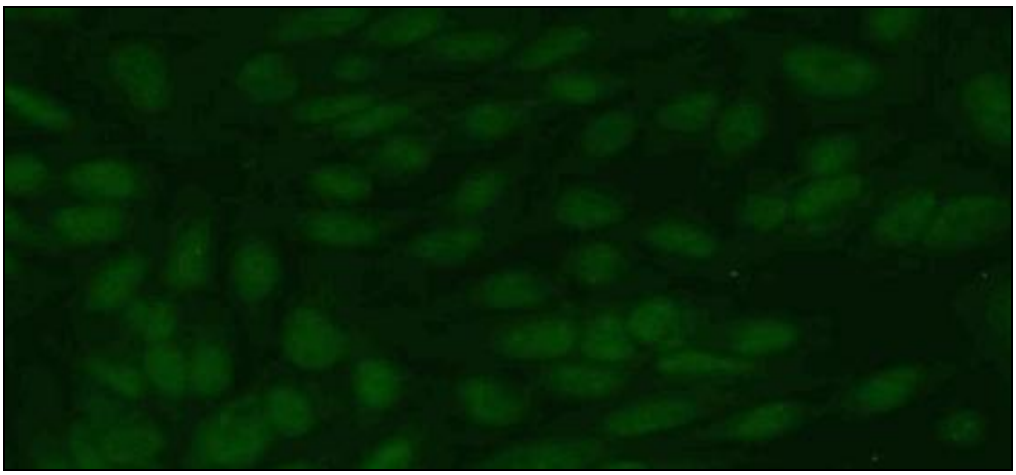

FIG. 4: ANA: IMMUNOFLUORESCENCE MICROSCOPY USING HUMAN CELLULAR EXTRACTS LIKE HEP-2 CELLS

Based on the correlation of USG, CECT Abdomen, laboratory investigations, and immunoserological reports, the disease was finally diagnosed.

After a two-year struggle with jaundice, the patient was correctly diagnosed in May with decompensated chronic liver disease (DCLD) related to autoimmune hepatitis with portal hypertension. The prescribed medications included T. UDCA 300mg, T. Ranitidine 150mg, T. Aldactone 25mg, T. LA, T. Spironolactone 25mg, and Syr. Lactulose 10ml. By June, the patient's liver condition had worsened, necessitating immediate registration for a liver transplant. At that time, the MELD Score was noted to be 19. Without delay, the patient was started on combination therapy with T. Prednisolone 5mg and T. Azathioprine 25mg.

The patient, who had been registered for liver transplantation, underwent a comprehensive transplant workup, which included a preoperative liver transplantation assessment. During this assessment, specialists from various fields evaluated and approved the patient for liver transplantation. The specialties involved in the

assessment included nephrology, cardiology, pulmonology, neurology, psychiatry, ENT, ophthalmology, diabetology, dental surgery, haematology, and endocrinology.

Additionally, it was noted during the assessment that the patient had chronic generalized gingivitis. Treatment for this condition included scaling to address the gingival health prior to the transplantation procedure. The medications followed were T. Prednisolone 5mg, T. Azathioprine 25mg, T. UDCA 300mg, T. Aldactone 25mg, T. Ranitidine 150mg advised for 14 days followed with addition of Syr. Lactulose 15ml. In August, the MELD score was re-evaluated and revealed a significant increase to 24. Consequently, the medication regimen was adjusted to include T. Spironolactone 25mg and T. Furosemide 40mg, with T. Lasix 40mg given as an alternative.

During the next hospital visit, the patient reported no active complaints. However, additional medications for expected seasonal illnesses were prescribed, including T. Levocetirizine 10mg, T. Azithromycin 500mg, and Syr. Asthakind. By November, the patient was admitted to the hospital with chief complaints of loose stools (5 to 6 times/day) for 3 days, fever, giddiness, multiple episodes of vomiting, and abdominal pain. The patient was kept under observation and treated with T. Aldactone 25mg, T. Prednisolone 5mg, T. Azathioprine 25mg, T. Ranitidine 150mgand T. UDCA 300mg. These medications were continued after discharge.

In December, the patient was re-admitted to the hospital with acute gastroenteritis, presenting with high-grade fever, chills, rigors, and loose stools (10 episodes/day). The patient was kept under observation and the same medications were continued, with the addition of T. Ciprofloxacin 500mg, Cap. Doxycycline 100mg, Cap. Bifilac, and T. Metronidazole 200mg. The patient's symptoms improved, leading to discharge with the continuation of the prescribed medications.

Clinical Status of the Patient in 2024: By early 2024, the patient's symptoms had improved, and no new complaints were observed. However, in February, the patient was admitted to the hospital with pedal edema, abdominal distension, intermittent fever, chills, rigor, abdominal pain, and loose stools, all persisting for four days. The laboratory findings (**Table 5**) were found to be progressive.

TABLE 5: THE LABORATORY FINDINGS FOR THE PERIOD OF 2024

Year	Month	Laboratory findings										
		Liver Function Test							Urine Analysis			
			Bilirubin		SGOT	SGPT	S. A. P	GGT	Bile salt	Bile pigment	Albumin	Globulin
		Total	Direct	Indirect								
2024	January	6.7 mg/dl	4.8 mg/dl	2.8 mg/dl	65 U/L	35 U/L	184 IU/L	79 U/L	Present	Positive	Nil	Nil
	February	12.1 mg/dl	6.6 mg/dl	2.96 mg/dl	63 U/L	40 U/L	184.7 IU/L	79 U/L	Present	Positive	Nil	Nil

SGOT - Serum Glutamic-Oxaloacetic Transaminase; SGPT- Serum Glutamate Pyruvate Transaminase; S.A.P - Serum Alkaline Phosphatase; GGT- Gamma-Glutamyl Transferase.

The treatment regimen included Amp. Norad, T. UDCA 300mg, T. Rifaximin 550mg, T. Prednisolone 5mg, T. Azathioprine 25mg, T. Rantac, T. PARA, T. Pan, and Syr. Lactulose 15ml. Following progressive treatment, the patient requested discharge and was sent home with the following medications: T. Spironolactone 25mg, T. Furosemide 60mg, T. Azathioprine 50mg, T. Prednisolone 5mg, T. Ranitidine 150mg, Cap. Bifilac, and T. Lasix 40mg. In March, the patient was admitted to the hospital for the final time with complaints of loose stools (approximately 7 to 10 times/day) for the past three days, fever, and giddiness, but no abdominal pain. Despite being under observation, the patient passed away during the hospital stay.

DISCUSSION: Autoimmune hepatitis (AIH) is a chronic liver condition characterized by inflammation driven by elevated gamma globulins and specific autoantibodies targeting liver tissue. It stems from a complex interplay of genetic predisposition, environmental triggers, and immune dysfunction, often effectively managed with

immunosuppressive therapy. The study discusses AIH classification as Type I, typically associated with antinuclear (ANA) and/or smooth muscle antibodies (SMA), and Type II, marked by anti-liver kidney microsomal antibodies (anti-LKM1), affecting younger individuals more severely. The study discusses genetic susceptibility involving specific HLA alleles, varying across ethnic groups, while environmental factors such as certain medications and infections can induce AIH through mechanisms like molecular mimicry. Immune dysregulation leads to T-cell-mediated hepatocyte damage and a chronic inflammatory state characterized by interface hepatitis on histology. Similarly, A case study documents the first known instance of Type I autoimmune hepatitis (AIH) likely caused by occupational exposure to N,N-Dimethylformamide (DMF) in a previously healthy 31-year-old Korean man. AIH involves genetic predisposition and environmental factors like DMF, which may trigger autoimmune responses [69].

The GRACE study highlighted higher rates of urinary tract infections, multiple vaccinations, early initiation of oral contraceptives, and smoking among AIH patients, illustrating the complex interplay between genetics and environment in AIH development [70]. We present a rare case of autoimmune hepatitis in an adult male with a delayed diagnosis. Initially experiencing jaundice at 14, the patient managed symptoms with complementary and alternative medicines. At 32, he was diagnosed with jaundice again, showing liver dysfunction and portal hypertension. Scans indicated liver disease progression, leading to a visit to a private tertiary care hospital. Despite continued medications, the condition worsened, and at 33, further scans confirmed severe liver disease and splenomegaly.

This study discusses clinical presentation that varies from acute onset with jaundice, fatigue, and pruritus to asymptomatic cases discovered incidentally. These clinical presentations lead to diagnosis that relies on excluding other liver diseases due to the absence of a pathognomonic marker, supported by elevated liver enzymes, immunoglobulin levels, and characteristic autoantibodies. In our case, by age 34, the patient faced increased symptoms, prompting a consultation at a government tertiary care hospital. After a thorough evaluation, the patient was diagnosed with decompensated chronic liver disease related to autoimmune hepatitis. The diagnosis was not timely and appropriate. Similarly, in another case, a patient with diffuse liver lesions initially suspected to be cancerous was found to have bridging necrosis on biopsy, ruling out malignancy. The patient was later diagnosed with acute autoimmune hepatitis (AIH) due to hypergammaglobulinemia and a negative etiological workup. AIH can resemble viral hepatitis or drug-induced liver injury, making accurate histological diagnosis crucial. Early recognition and treatment of AIH with steroids are essential to prevent potentially fatal outcomes[71]. This study also discusses about novel diagnostic approaches including neuro-fuzzy cognitive maps, serum biomarkers like GDF15, and gene expression profiling, aiming to improve accuracy and early detection.

Treatment strategies discussed encompass initial induction with prednisone and azathioprine to achieve remission, followed by maintenance therapy to sustain disease control while minimizing steroid-related side effects. For refractory cases, alternative immunosuppressive agents like mycophenolate mofetil or calcineurin inhibitors may be employed. Liver transplantation remains an option for end-stage disease or acute liver failure cases. Our patient was started with steroids after delayed diagnosis and registered for liver transplantation. A qualitative study on autoimmune hepatitis (AIH) revealed significant impacts on patients' quality of life, including challenges in work, relationships, social activities, diet, and exercise. Fatigue was particularly debilitating, leading to anxiety and depression.

Participants expressed frustration with healthcare providers' understanding of AIH and the associated stigma, emphasizing the need for better symptom management and increased awareness among healthcare professionals to improve their quality of life [72]. This study discusses ongoing research that explores novel therapeutic avenues such as cytokine modulation and immunoproteasome inhibition to further optimize treatment outcomes. Our study includes understanding of risks associated with AIH, including disease recurrence and potential complications from vaccinations like

COVID-19 and Hepatitis A, underscores the importance of tailored management strategies and ongoing patient monitoring. This holistic approach aims to improve clinical outcomes and quality of life for individuals affected by autoimmune hepatitis. A study on hepatocellular carcinoma (HCC) in autoimmune hepatitis (AIH) patients found that overall survival was favourable but significantly lower for those with HCC. Key risk factors included cirrhosis at diagnosis, diabetes, and persistent abnormal liver enzymes. Management strategies recommend regular imaging and alpha-fetoprotein monitoring for high-risk patients and caution with immune checkpoint inhibitors. The study underscores the need for further research on therapeutic options, especially molecularly-targeted drugs, due to limited treatments for AIH-related HCC [73].

In our case, despite adjustments to medication and intensive monitoring, his condition deteriorated, leading to hospital admissions for severe symptoms. In early 2024, despite improvement, he was admitted again and, ultimately, passed away during the hospital stay. The patient's case underscores the critical importance of accurate diagnosis and timely treatment. Had the patient received proper diagnosis and timely medical intervention at the initial hospitals visited, it is possible their life expectancy could have been extended significantly. Negligence and inadequate expertise in some medical facilities can result in overlooked diagnoses of rare conditions like this, leading to unnecessary loss of life for many patients who remain unaware of their illnesses.

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