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Diagnostic and clinical characteristics of liver autoantibodies by immunoblot in a medical laboratory

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Abstract

Background: Autoimmune liver diseases (ALD) are a heterogeneous group of disorders affecting the hepatobiliary system and are characterized by specific autoantibodies. These are routinely measured in diagnostic laboratories using commercial line immunoblot (LIB) assays. However, the ordering characteristics and diagnostic performance of this test have not been extensively evaluated. This study aims to examine the performance of the ALD LIB in a single diagnostic laboratory.

Methods: A retrospective, cross-sectional audit of 12 months of data was performed at the Institute of Clinical Pathology and Medical Research diagnostic laboratory (Westmead Hospital, Australia). Patients referred for an ALD-LIB were included. Medical notes were reviewed to ascertain the clinical diagnoses of patients. Patients who had at least one positive ALD autoantibody on LIB were defined as "blot-positive" and compared with "blot-negative" patients. The performance of the ALD-LIB was assessed through the calculation of diagnostic sensitivities and specificities.

Results: There were 611 patients included over the 12-month period. Sixty-four of these patients (10%) were blot-positive. These patients were more likely to be female, to have other ALD-associated autoantibodies, and to have lower alkaline phosphatase (ALP) levels compared with blot-negative patients. An ALD diagnosis or systemic autoimmune disease was more likely to be identified in blot-positive patients. Finally, the LIB demonstrated a high negative predictive value for an ALD diagnosis in this patient cohort.

Conclusion: This real-world analysis of the laboratory's ALD-LIB provided insights into the ordering characteristics and performance of this assay in patients referred for testing. When combined with other ALD investigations, the ALD-LIB is a useful adjunct in the evaluation of patients with suspected ALD.

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Introduction

Autoantibodies are among the most important biomarkers in autoimmune diseases, particularly with respect to their diagnosis (1). They reflect autoreactive B cells, the failure of immunological tolerance and are often of the IgG isotype. There are a variety of methods for detecting autoantibodies in the diagnostic laboratory, including line immunoblot (LIB), indirect immunofluorescence (IIF), enzyme-linked immunosorbent assay (ELISA), and radioimmunoassays (2). The LIB has a number of antigens impregnated on nitrocellulose strips, allowing the simultaneous detection of multiple autoantibodies. Positive results are visualised as dark bands, which may be objectively read using a scanner and software. Densitometry values that exceed a pre-defined cut-off are deemed positive or detected.

Some autoimmune diseases that benefit from the detection of autoantibodies in their diagnosis are the autoimmune liver diseases (ALDs). ALDs encompass a group of diseases, namely autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC), which have distinct or sometimes overlapping clinical and laboratory features (3). They affect approximately 1 in 100,000 people and are characterised by key serum autoantibodies (3). AIH is characterised by hepatitis/transaminitis, polyclonal hypergammaglobulinaemia, and autoantibodies to smooth muscle (F-actin), soluble liver antigen/liver pancreas (SLA/LP) (type I AIH), or liver–kidney microsomes-1 (LKM1) (type II AIH). PBC is characterised by destruction of the biliary system, resulting in cholestasis, liver cirrhosis, and the presence of anti-mitochondrial antibodies (AMA) and sp100. PSC is a disorder resulting from inflammation of the bile ducts; although multiple antigenic targets have been identified, distinct disease-specific autoantibodies have not yet been reported (4).

Although some ALD autoantibodies may be detected by IIF through distinct staining patterns on tissues, the LIB offers multiplex detection of autoantibodies that may not produce a distinct IIF pattern. Despite the availability of commercial LIBs, there are no studies examining the ordering characteristics and clinical diagnoses of patients who undergo an ALD-LIB. Furthermore, to our knowledge, no studies have evaluated the "real-world" performance of this LIB in a laboratory or hospital cohort. This is particularly important, as LIBs have been criticized for limitations such as lack of diagnostic specificity and high costs (5,6). Additionally, LIB results do not always reliably correlate with immunofluorescence patterns, particularly when the autoantibody is present at low concentrations (7). Therefore, the aim of this study was to examine the diagnostic performance and characteristics of a commercial ALD-LIB in a single-center major immunology laboratory in Western Sydney, Australia.

Methods

Patients

The immunology diagnostic laboratory at Westmead Hospital serves the population of Western Sydney. A cross-sectional, observational study was conducted over a 12-month period from 2020 - 2021 at Westmead Hospital, Australia. Consecutive patients who were referred for testing of ALD autoantibodies and had a LIB performed were included. The census date for the review of medical records was 30 June 2023. The median follow-up time was 4.0 years. As this was a laboratory quality assurance exercise, consent was not obtained from individual patients, and the project was approved by the Western Sydney Local Health District Research Office (Approval 2010-07QA).

Autoantibody assays

The ALD LIB (Euroimmun, Germany) was performed according to the manufacturer's instructions and analysed as previously described (8). Serum was diluted 1:100, and a positive result was defined as >10 units, as recommended by the manufacturer (8). The assayed autoantibodies were IgG directed towards AMA-M2, M2-3E, sp100, promyelocytic leukaemia antigen (PML), gp210, LKM-1, liver cytosol (LC)-1, soluble liver antigen (SLA), and Ro52. AMA, smooth muscle antibodies (SMA), LKM antibodies, and antinuclear antibodies (ANA) were assessed by indirect immunofluorescence (IIF) microscopy (All on commercial slides from Euroimmun) and screened at serum titres of 1:40, 1:40, 1:40, and 1:80, respectively. IIF evaluations were arbitrated by two independent experienced scientists, with a third senior reader involved if any discordance was not resolved by discussion.

Statistics

SPSS for Windows version 22 was used to calculate statistics. For categorical and binary variables, differences were calculated using Fisher's exact test (With assumption checking), as some sample sizes were < 5. Continuous variables were assessed using the Shapiro-Wilk normality test, and differences were determined using Student's t-test or the Mann-Whitney test, as appropriate. A P-value of < 0.05 was considered statistically significant. Diagnostic statistics (Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)) were calculated according to standard formulae (9) for the diagnosis of ALD, defined by a positive liver biopsy and a compatible clinical picture. The MedCalc statistics online calculator was used to calculate 95% confidence intervals (10). Since all patients consecutively referred for an ALD-LIB were included in the analyses, there were no relevant missing data variables in the demographic information. Missing clinical notes (Diagnoses) were not mathematically imputed due to the risk of geographical bias; however, there were no differences in the proportion of missing notes between the patient cohorts (Table 1).

Table 1. Diagnoses of patients receiving an autoimmune liver autoantibody line immunoblot in the audit period

Clinical diagnosis (n)	**Blot negative *n* = 547[a] *n* (% of blot negative)**	**Blot positive *n* = 64 *n* (% of blot positive)**	**P-value**
Missing/Insufficient clinical notes (291)	256 (46.8)	35 (54.7)	0.237
No diagnosis established (61)	53 (9.7)	8 (12.5)	0.507
Autoimmune liver/Biliary disease (26)	13 (2.4)	13 (20.3)	**< 0.001**
Alcoholic liver disease (33)	31 (5.7)	2 (3.1)	0.563
Amyloidosis (2)	1 (0.18)	1 (1.6)	0.199
Cardiac-related liver disease (5)	4 (0.7)	1 (1.6)	0.426
Gall bladder/Bile duct disease (10)	10 (2.4)	0 (0)	0.610
Cryptogenic cirrhosis (4)	4 (0.73)	0 (0)	1.000
Drug-induced hepatitis (22)	21 (3.8)	1 (1.6)	0.719
Fatty liver disease (63)	57 (10.4)	6 (9.4)	1.000
Graft-versus-host disease (3)	3 (0.6)	0 (0)	1.000
Haemochromatosis (2)	1 (0.2)	1 (1.6)	1.000
IgG4 disease (2)	2 (0.4)	0 (0)	1.000
Non-viral infective hepatitis (11)	9 (1.7)	2 (3.1)	0.323
Ischemic hepatitis (8)	8 (1.5)	0 (0)	1.000
Malignancy (25)	21 (3.8)	4 (6.3)	0.320
Miscellaneous (15)	11 (2.0)	4 (6.3)	0.062
Myositis (3)	3 (0.6)	0 (0)	1.000
Pancreatitis (2)	2 (0.4)	0 (0)	1.000
Pregnancy-related (3)	2 (0.4)	1 (1.6)	0.283
Other systemic autoimmune diseases e.g., SLE (12)	4 (0.7)	8 (12.5)	**< 0.001**
Viral hepatitis (36)	31 (5.7)	5 (7.8)	0.572

[a] Data is presented as n (%). SLE, systemic lupus erythematosus. Comparison of proportions according to blot positivity was performed using Fisher's exact test with assumption checking. Bolded p-values represent values < 0.05 (Significant).

Results

During the 12-month period, there were 652 patient requests for liver autoantibodies by LIB. The precision (Inter-assay variation) of the ALD-LIB was assessed using a pooled internal serum sample included in each run. The inter-assay coefficients of variation (CV) were 8.9% for anti-Ro52, 2.3% for anti-SLA/LP, 6.8% for anti-LC1, 17.5% for anti-LKM-1, 6.5% for anti-gp210, 11.5% for anti-PML, 12.5% for anti-Sp100, 5.0% for anti-M2-3E, and 14.6% for anti-M2, resulting in an overall CV of 9.5%.

After removing 13 duplicate or serial requests, 639 individual patients remained in the audit period. Clinical and medical notes were reviewed to determine the reasons for requesting ALD autoantibodies. Valid or sufficient notes were available for 462 patients (72%). The most common reasons for requesting these autoantibodies were deranged liver function tests (LFTs) (334, 72%), work-up for liver cirrhosis (49, 11%), suspected ALD (30, 6%), and active or chronic hepatitis (27, 6%).

We defined blot-positive patients as any patient in the audit period who had at least one positive autoantibody on the liver blot. There were 92 blot-positive patients (14%). Given that anti-Ro52/TRIM21 is a non-specific autoantibody found in a range of autoimmune and non-autoimmune disorders (11), we excluded blot-positive patients who were monopositive for anti-Ro52/TRIM21 (Positive for anti-Ro52/TRIM21 with no other liver autoantibody positivity) to minimize bias in the blot-positive patient subset. This left 611 patients for subsequent analyses.

Of these 611 patients, 64 (10%) were blot-positive. They comprised 24 patients (38%) with M2-3E antibodies, 20 (31%) with gp210, 16 (25%) with AMA-M2, 16 (25%) with Ro52, 15 (23%) with sp100, 11 (17%) with LC-1, 6 (9%) with PML, 4 (6%) with SLA/LP, and 3 (5%) with LKM-1. Figure 1 summarises the inclusion and exclusion of study patients. In general, patients who were blot-positive tended to be female, have concomitant autoantibodies (AMA, SMA, and ANA), have lower alkaline phosphatase (ALP) levels, and exhibit greater hypergammaglobulinaemia (Table 2).

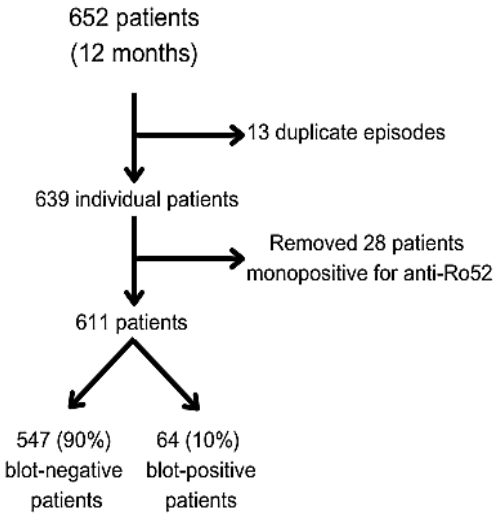

Figure 1. Flowchart of the inclusion and exclusion of patients in the 12-month study period

Medical notes were reviewed to determine the final diagnosis, with at least 2 years of follow-up notes after the initial ALD autoantibody request. A diagnosis explaining the liver disease and/or autoantibody result was established in 348 cases (54%). There were 26 cases (7%) of biopsy-confirmed AIH/autoimmune biliary conditions, comprising 14 AIH cases, 11 PBC cases, and 1 overlap AIH/PBC/PSC condition. As expected, a positive ALD-LIB was more likely to be observed in patients with an established diagnosis of ALD or other systemic autoimmune diseases, such as systemic lupus erythematosus (SLE) (Table 1). Of the 64 blot-positive patients, 35 (55%) had sufficient medical notes available to ascertain their diagnoses. These included PBC (7, 20%), fatty liver disease (4, 11%), SLE (4, 11%), and AIH (3, 9%). For patients diagnosed with ALD disorders, the detected autoantibodies were M2-3E (8 patients), AMA-M2 (6), Ro52/TRIM21 (6), LC1 (3), sp100 (3), and gp210 (1). No autoantibodies to SLA/LP, LKM-1, or PML were detected

in any of the patients during the study period. Overall, there was a diagnostic accuracy of 20.3% for blot-positive patients (Table 1), reflecting the fact that these autoantibodies may be found in pathologies other than ALD (12) and/or may precede the clinical emergence of an autoimmune disorder.

Next, we determined the diagnostic performance of the detection of AIH-associated autoantibodies in the laboratory context (Table 3). Antibodies to LKM-1 and PML were excluded from the analyses, as there were no occurrences of these autoantibodies during the audit period on the ALD-LIB. In addition, only 4 anti-SLA-LP cases were detected, which were insufficient to perform meaningful analyses; therefore, these were also excluded. The evaluated antibodies demonstrated consistently high diagnostic specificities and high negative predictive values for any ALD diagnosis (Table 3).

To examine the analytical performance of the ALD-LIB, we assessed concordant IIF staining on corresponding rodent and HEp2 tissue substrates as our "gold standard" assays (13). We evaluated liver-specific autoantibodies to AMA-M2, M2-3E, Sp100, gp210, and LC-1 and examined the corresponding tissue substrates for concordant IIF staining (Table 4). Overall, there was high agreement between IIF and the detected ALD-LIB antibodies, particularly for mitochondrial antibodies (Table 4), indicating relatively good analytical performance of the ALD-LIB assay. It was not possible to calculate analytical sensitivities and specificities due to the study design.

Table 2. Comparison of blot-negative and blot-positive patients in the 12-month audit period

Parameter	Blot negative *n* = 547	Blot positive *n* = 64	P-value
Female n (%)	297 (54)	48 (75)	**0.001**
Age (Year) median (IQR)[a]	51.7 (28.0)	56.0 (29.0)	**0.025**
AMA (*n*, %)	4/351 (1)	14/41 (22)	**< 0.001**
SMA (*n*, %)	41/373 (8)	12/38 (19)	**0.001**
LKM (*n*, %)	1/259 (0)	0/31 (0)	1.000
ANA (*n*, %) Cytoplasmic Nuclear/mitotic pattern	 30/407 (7) 197 (48)	 7/45 (16) 33/45 (73)	**< 0.001**
Alanine transaminase (Median U/L [IQR]) [a]	241.5 (166.0)	224.9 (53.0)	0.110
Aspartate aminotransferase (Median U/L [IQR]) [a]	198.3 (136.0)	230.0 (76.0)	0.623
Gamma-glutamyl transferase (Median U/L [IQR]) [a]	242.2 (302.0)	215.2 (225.0)	0.414
Alkaline phosphatase (Median U/L [IQR]) [a]	219.2 (212.0)	145.9 (138.0)	**0.017**
Albumin (Mean g/L [SD]) [b]	34.0 (7.2)	34.9 (7.2)	0.731
Bilirubin (Median umol/L [IQR]) [a]	28.7 (29.0)	28.5 (21.0)	0.913
IgG (Median g/L [IQR]) [a]	12.7 (6.9)	16.5 (8.4)	**0.005**
International normalised ratio (Median [IQR]) [a]	1.2 (0.3)	1.3 (0.4)	0.686

Abbreviations: *IQR*, Interquartile Range. *SD*, Standard Deviation. *AMA*, Antimitochondrial Antibody. *SMA*, Smooth Muscle Antibody. *LKM*, Liver Kidney Microsomes. *ANA*, Antinuclear Antibody.
[a] Shapiro-Wilk test demonstrates non-normal distribution ($P < 0.001$) so Mann-Whitney U test was used to analysed differences. [b] Shapiro-Wilk demonstrates approximately normal distribution ($P = 0.078$), and differences in mean was analysed by Student's t-test. Bolded P-values represent values < 0.05 (Statistically significant).

Table 3. Diagnostic performance of liver autoantibodies measured by line immunoblot for the diagnosis of autoimmune liver disorders

Autoantibody	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Ro52	23.1 (9.0 - 43.6)	93.8 (91.6 - 95.6)	13.6 (6.8 - 25.4)	96.6 (95.9 - 97.3)
Liver cytosol-1	11.5 (2.5 - 30.2)	98.7 (97.4 - 99.4)	27.3 (9.6 - 57.1)	96.3 (95.8 - 96.8)
gp210 (20)	3.9 (0.1 - 19.6)	96.9 (95.2 - 98.1)	5.0 (0.7 - 27.4)	96.0 (95.7 - 96.3)
Sp100 (15)	11.5 (2.5 - 30.2)	98.0 (96.6 - 99.0)	20.0 (7.0 - 45.4)	96.3 (95.8 - 96.8)
M2-3E (24)	30.8 (14.3 - 51.8)	97.4 (95.8 - 98.5)	33.3 (19.1 - 51.5)	97.1 (96.3 - 97.7)
AMA-M2 (16)	23.1 (9.0 - 43.7)	98.4 (97.0 - 99.2)	37.5 (19.1 - 60.4)	96.8 (96.1 - 97.4)

AMA, Antimitochondrial Antibodies.
Values are percentages (95% confidence interval).

Table 4. Positive liver immunoblot cases and their concordance with corresponding indirect immunofluorescence (IIF) microscopy

IgG (n of cases with corresponding tissue IIF)	IIF staining pattern	Concordance with IIF N (%)
AMA-M2 (15)	Staining of renal tubules, hepatocytes and gastric parietal cells on rodent tissue	14/15 (93)
M2-3E (24)	Staining of renal tubules, hepatocytes and gastric parietal cells on rodent tissue	22/24 (92)
Sp100 (12)	Multiple nuclear dots on HEp2 substrate	11/12 (92)
gp210 (20)	Rim-like / nuclear membrane on HEp2 substrate	15/20 (75)
Liver-cytosol 1 (10)	Hepatocyte staining sparing central vein on rodent liver	8/10 (80)

Discussion

Although ALDs are a rare group of disorders, they are important to recognise and diagnose. The ALD-LIB is frequently used to aid in the diagnosis of ALD in the clinical setting. In this study, we analysed the ordering patterns and patient characteristics of those tested using the ALD-LIB in a tertiary hospital immunology laboratory in Western Sydney. As expected, the majority of patients referred for ALD-LIB testing had deranged liver function tests (LFTs) or a liver disorder requiring investigation. However, only 7% of these patients had a biopsy-confirmed ALD diagnosis.

Our findings showing associations between female sex, increased hypergammaglobulinaemia, and lower alkaline phosphatase (ALP) levels with positive ALD autoantibodies (Table 2) may reflect the fact that approximately two-thirds of ALD patients in our cohort were diagnosed with AIH. AIH is one of the most common ALDs and is characterised by a female predominance, hypergammaglobulinaemia, and relatively normal or mildly increased ALP levels (14). Furthermore, the presence of ALD autoantibodies in other autoimmune conditions (Table 1) likely reflects the concomitant occurrence of ALD in other connective tissue diseases (15). The high prevalence of autoantibodies in non-ALD conditions may indicate either undiagnosed ALD - since not all patients with deranged LFTs undergo liver biopsy - or the genuine induction of autoantibodies secondary to underlying pathology (12).

Consistent with the performance of other disease-specific autoantibodies (16), ALD autoantibodies detected by LIB are more useful for ruling out ALD when negative, as reflected by the high negative predictive value (NPV) (Table 3). Marked differences in sensitivities and specificities among the autoantibodies were observed for the diagnosis of ALD. This may be because not all patients with ALD have detectable liver-specific autoantibodies, whereas these autoantibodies are almost exclusively associated with ALDs. The low positive predictive values (PPV) observed across the autoantibodies (Table 3) likely reflect the relatively low prevalence of ALD in this patient cohort (7%) (Table 1).

It has been suggested that IIF microscopy on relevant tissues is more optimal for screening for ALD autoantibodies (14). Indeed, according to the International Autoimmune Hepatitis Group, the reference standard for measuring these autoantibodies is the IIF method (17). A meta-analysis determined that ANA and SMA have moderate diagnostic sensitivity, at around 60%, for AIH (18). In another meta-analysis, AMA detected by IIF had a high diagnostic sensitivity of 85% for the diagnosis of PBC (19). Therefore, the ALD-LIB serves to confirm IIF findings, for which there is generally good correlation between the two methods (20). However, some suggest that when there is a high index of suspicion for a particular ALD-associated autoantibody or ALD, testing for specific antigens provides the most sensitive method to confirm or refute this (21).

Autoantibodies are also particularly important in subtyping AIH, with LKM autoantibodies being the hallmark of AIH type 2, for instance (14). They may also be useful for prognosticating ALD patients. For example, autoantibodies to Ro52/TRIM21 are independent risk factors for end-stage liver disease (22). This highlights the importance of accurate detection of these autoantibodies by LIB in routine clinical practice. However, concerns have been raised regarding the diagnostic and analytical specifications of LIBs in clinical practice (6). A previous evaluation of the same ALD-LIB tested in a cohort of AIH/PBC patients revealed a surprising number of healthy controls testing positive for ALD-associated autoantibodies, such as anti-M2, anti-gp210, and anti-LC-1, using the manufacturer's suggested cut-off (23,24). Increasing the cut-off values for multiple autoantibodies was possible without compromising the diagnostic sensitivity of the LIB (23). Therefore, although there are multiple advantages to using a multiplex ALD-LIB, it is vital that results are correlated with the patient's clinical situation (6) and that the laboratory establishes its own local reference ranges (25).

This study has several important limitations. First, it was conducted at a single center in Australia with specific patient demographics and a particular prevalence of ALDs. This would affect the prevalence of ALD and, consequently, the NPV and PPV (Table 3). Therefore, the generalisability of these findings should be interpreted with caution and ideally replicated in other studies. In addition, the cohort in this study represented a general laboratory population rather than a dedicated cohort of ALD patients and healthy controls. This may account for the high proportion of missing clinical notes and medical records (Table 1), as patients were referred from multiple hospitals and clinics, including private clinics. It is possible that patients with sufficient documentation were more likely to belong to certain clinics or to have particular diagnoses. This represents a major source of bias in the study.

We also lacked the presence of certain autoantibodies on the LIB and therefore had a limited cohort. For example, there were no detectable LKM-1 antibodies on the ALD-LIB during the audit period, despite this being one of the most important and specific autoantibodies for typing AIH. This may be explained by the relatively low prevalence of these antibodies in AIH patients (26) and the small number of biopsy-proven AIH diagnoses (Table 1). Nevertheless, we believe our study reflects the "real-world" context of ALD-LIB testing, as it was conducted within a laboratory cohort attached to a tertiary hospital. Furthermore, although the inclusion of a healthy control cohort would have been helpful, this may have artificially elevated the performance characteristics of these autoantibodies due to their low prevalence in healthy individuals (12). Ideally, well-defined disease control comparison groups (e.g., cirrhosis, fatty liver disease, etc.) should be included, as ALD-related antibodies may occasionally be detected in these groups and/or precede the development of ALD.

Conclusion

In summary, 10% of patients referred for an ALD-LIB were positive and tended to be diagnosed with AIH. In a laboratory context, ALD-associated autoantibodies detected by LIB demonstrated low sensitivity but high specificity for the diagnosis of ALD. Suitable avenues for future research include evaluating these autoantibodies in the context of specific diagnoses (e.g., AIH vs. PBC) and examining correlations between LIB specificities and detailed clinical parameters.

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Ethical statement

This study was approved by the WSLHD Research Office (Approval 2010-07QA).

Conflicts of interest

The author has no relevant financial or non-financial interests to disclose.

Author contributions

A. Y. S. L. contributed to study conception and design, data collection, analysis, and drafting of the manuscript.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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