Hepatic Abnormalities in Patients with Chronic Granulomatous Disease

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ABSTRACT

Chronic granulomatous disease (CGD) is a rare congenital disorder characterized by repeated bacterial and fungal infections. Aside from a high incidence of liver abscess, little is known about hepatic involvement in CGD. The aim of this study was to describe the spectrum of liver abnormalities seen in CGD. The charts of 194 patients with CGD followed at the NIH were reviewed, with a focus on liver abnormalities. Liver enzyme elevations occurred on at least one occasion in 73% of patients during a mean of 8.9 years of follow-up. ALT elevations were generally transient. Although transient alkaline phosphatase (ALP) elevations were also common, persistent ALP elevations lasting up to 17.6 years were seen in 25% of patients. Liver abscess occurred in 35% of patients. Drug-induced hepatotoxicity was documented in 15% of patients but likely occurred more frequently. Hepatomegaly was found in 34% and splenomegaly in 56% of patients. Liver histology showed granulomata in 75% and lobular hepatitis in 90% of specimens. Venopathy of the portal vein was common (80%) and associated with splenomegaly. Venopathy of the central vein was also common (63%) and was associated with the number of abscess episodes. Nodular regenerative hyperplasia (NRH) was seen in 9 patients, including 6 of 12 autopsy specimens. Conclusion: Liver enzyme abnormalities occur frequently in patients with CGD. In addition to liver abscesses and granulomata, drug hepatotoxicity is likely underappreciated. Vascular lesions such as venopathy and—to a lesser extent—NRH are common. The cause and clinical consequences of venopathy await prospective evaluation.

INTRODUCTION

Chronic granulomatous disease (CGD) is a rare inherited disorder occurring in 1 in 250,000 individuals.[1] The underlying defect is a loss or inactivation of a component of the reduced NADPH complex, resulting in a defective oxygen metabolic burst with inadequate production of superoxide and peroxide and, perhaps most importantly, an inability of phagocytic cells to kill certain bacteria and fungi.[2] These defects predispose affected individuals to recurrent infectious complications and significantly reduced long-term survival.[3]

Four principal CGD genotypes have been described, with important differences in phenotypic expression. Because the $gp91^{phox}$ genotype is X-linked and accounts for 70% of patients in large cohort studies, CGD has a significant male predominance.[4] The other described genotypes, ^{p22phox}, $p47^{phox}$, and $p67^{phox}$, are autosomal recessive.[4] In addition to being more common, X-linked CGD ($gp91^{phox}$) portends a worse prognosis with a higher annual mortality compared with the other genotypes.[1] The reduced NADPH is composed of cell membrane ($p22^{phox}$, $gp91^{phox}$) or cytoplasmic moieties ($p47^{phox}$, $p67^{phox}$).[1]

Although pulmonary infections predominate in CGD, with 79% of a 368-patient registry reporting a history of pneumonia, other sites are also commonly affected, including suppurative adenitis (53%), subcutaneous abscess (42%), liver abscess (27%), and osteomyelitis (25%).[5] Catalase-positive organisms are particularly problematic in CGD, because they are thought to prevent impaired CGD phagocytes from using microbial hydrogen peroxide.[5] Staphylococcal species are the most common organisms seen, particularly in liver abscesses, where they account for over 50% of infections.[6] Gram-negative rods (Serratia marcescens, Burkholderia cepacia) and fungi (Aspergillus species) are also commonly reported.[6]

Liver abscesses typically present with fever with or without abdominal pain and are often accompanied by constitutional symptoms. In patients with CGD, abscess recurrence usually results from new primary infection rather than relapse.[6] Radiological findings of abscess may differ in CGD, as described recently.[7] Aggressive surgical management has been shown to be more effective than medical intervention alone for large abscesses, reducing the mortality from 27% to 6%.[8,9]

With earlier diagnosis, IFN-γ and antimicrobial prophylaxis, and aggressive surgical and medical management, mortality for patients with CGD has plummeted in just a few decades with many patients now surviving well into adulthood.[9,10] Aside from the association with liver abscess, little is known about liver disease in CGD. Because patients are living longer, the consequences of recurrent hepatic abscesses, complicated and prolonged courses of antimicrobials, and often-large hepatic resections may become more relevant. The goal of this retrospective study was to define the spectrum of liver disease and hepatopathology in a large cohort of well-characterized patients with CGD.

PATIENTS AND METHODS

A large cohort of patients with CGD has been followed at the Clinical Center of the NIH as part of a natural history protocol. All patients had the diagnosis of CGD

confirmed by either nitroblue tetrazolium reduction or dihydrorhodamine oxidation.[11] The specific gene defect was determined via immunoblotting, sequencing, or both whenever possible. All available patient charts as well as laboratory, pathological, microbiological, and radiological data were reviewed.

All radiological studies were reviewed by an abdominal radiologist with particular attention to liver contour and size, hepatic calcifications, abscesses, portal hypertensive changes, and spleen size. Hepatomegaly and splenomegaly were determined in relation to body size. A dedicated hepatopathologist reviewed all liver biopsy and wedge resection specimens. All histological specimens were examined at least 2 cm distant from liver abscesses to avoid reporting of peri-abscess changes.

Because data were collected longitudinally, liver enzyme elevations were categorized based on the predominant pattern over time. Enzyme elevations returning to baseline or normal within 3 months were deemed transient rises, while those persisting for longer than 3 months were defined as persistent. All enzyme elevations were recorded in relationship to normal values: normal, 1-2 times the upper limit of normal (ULN), 2-5 times ULN, 5-10 times ULN, and >10 times ULN. Because alkaline phosphatase (ALP) is elevated in childhood due to bone growth, for patients 14 years or younger, a ULN of ALP of 400 IU/L was used, and thereafter evaluations were based on the adult ULN value of 116 IU/L. In the majority of cases, ALP elevations were confirmed to be of liver origin by a corresponding elevation of γ-glutamyltranspeptidase on at least one occasion. The following definitions were used to define liver enzyme patterns:

1. Persistent hepatocellular injury: ALT ≥ULN for >3 months with ALP elevation of ≤ 1 category of elevation below that of ALT (e.g., ALT 2-5X for 6 mo with ALP ≤ 1-2X ULN).
2. Transient hepatocellular injury: ALT elevation ≥ 2 category difference more than ALP elevation (e.g., ALT >10X ULN with ALP ≤ 2-5X ULN) with spontaneous return to normal or previous baseline within 3 months.
3. Persistent cholestatic injury: ALP ≥ ULN for >3 months with ≤ 2 flares of ALT to equal category of ALP elevation (e.g., ALP 2-5 X ULN for 6 mo with ≤2 ALT flares to 2-5X ULN).
4. Transient cholestatic injury: ALP elevation ≥ 2-category difference more than ALT elevation (e.g., ALP >10X ULN with ALT ≤ 2-5X ULN) with spontaneous return to normal or previous baseline within 3 months.
5. Persistent cholestatic injury with ALT flares: ALP ≥ ULN for >3 months with ALT flares beyond those described in category 3 (e.g., ALP 2-5X ULN with 5 ALT flares to 5-10X ULN).
6. Mixed injury: ALP and ALT with < 2-category difference of magnitude of elevation (e.g., ALT 1-2X ULN with ALP 2-5X ULN)
7. No significant elevation: ALP and ALT persistently in normal range or ≤ 2 elevations to ≤ 1-2X ULN during follow-up.

Previous reports in the literature define only individual values rather than longitudinal data. To better appreciate the effects of prolonged enzyme elevations over time, the above definitions were developed.

Categorical variables were compared using the χ^2 or Fisher exact test, and continuous variables were compared using the Student t test or one-way ANOVA. A *P* value of less

than 0.05 was considered statistically significant. Univariate and multivariate logistic regression were per-formed using SAS software.

RESULTS

A total of 194 patients with CGD were evaluated. The majority of patients were male (n = 150 [77%]) and most were Caucasian (n = 155 [80%]) (Table 1). Other ethnicities were also represented, including African American (n = 22 [11%]), Hispanic (n = 12 [6%]), Asian (n = 5 [2%]). The mean age at last follow-up was 19.5 years (range 1.3-63.9), and patients were followed for a mean of 8.9 years. The CGD genotype distribution was as follows: gp 91^{phox} n = 114 (59%), $p47^{phox}$ n = 56 (29%), $p22^{phox}$ n = 4 (2%), $p67^{phox}$, n = 3 (2%), and unknown, n = 17 (8%). Twelve patients (6%) had previously undergone bone marrow transplantation as curative therapy for CGD. A total of 23 patients died during follow-up, all of infectious complications.

Liver enzyme abnormalities were common, occurring in 141 (73%) patients on at least one occasion during follow-up. Various patterns of both ALT and ALP elevations were seen. The majority of ALT elevations were transient, returning to normal values within 3 months; however, 4 patients had persistent mild ALT elevations (1-2 X ULN) for up to 18.6 years. In contrast, 49 (25%) patients had persistent elevations of ALP (mean 198 IU/ L), 13 of which were at least 2-5 X ULN (mean 233 IU/L). The persistent ALP elevations lasted for a mean of 5.1 years (range 0.8-17.6), accounting for an average of 48% (range 7%-100%) of the duration of follow-up.

Transient ALT elevations occurred in 116 patients (60%) ranging from mild (< 2X ULN) to moderate (2-5X ULN) in 38 and 35 patients, respectively, while 43 (22%) patients had more significant ALT elevations (>5X ULN), including 25 (9%) patients with at least one ALT value of >10X ULN. Patients had a mean of 2.8 (range 0-26) ALT elevations or 0.51 (range 0-6.2) ALT elevations per year of follow-up.

Transient elevations of ALP were also common, occurring in 97 (50%) patients. Forty (21%) patients had only mild ALP elevations (1-2X ULN), while 37 (19%) had moderate (2-5X ULN) and 20 (10%) had severe (>5X ULN) ALP elevations. Seven (4%) patients had at least one ALP elevation to >10X ULN. On average, patients had 1.7 (range 0-23) elevations of ALP or 0.6 (range 0-25) elevations of ALP per year of follow-up.

The patterns of liver enzyme elevation were categorized as described in the methods section to take into account the fact that patients had multiple and often concomitant elevations of both transaminases and ALP. These categorizations provide a more general summary of the pattern of liver enzyme elevations over time. Using these definitions, 45 (23%) patients had a predominantly cholestatic pattern of elevation, 7 (4%) transient and 38 (20%) persistent. Of those with a persistent cholestatic pattern, 14 (37%) had significant ALT flares superimposed upon chronic ALP elevation. A predominantly hepatocellular pattern and a mixed pattern of elevation were each seen in 35 patients (18%). Seventy-nine patients (41%) had normal or near normal liver enzymes throughout follow-up.

Etiology

A small number of patients had coexisting liver disease not directly related to CGD. Four patients had antibodies to HCV, and 3 were positive for hepatitis C RNA. Two patients had chronic hepatitis B infection, 2 had nonalcoholic steatohepatitis on liver biopsy, 2 had chronic cholestasis secondary to total parenteral nutrition, and 2 had hepatic graft-versus-host disease as a com-plication of previous bone marrow transplantation. Although not directly related to CGD, it is notable that two of the HCV-infected patients likely acquired infection from contaminated blood products, and total parenteral nutrition as well as bone marrow transplant were used as treatment for complications of CGD.

Just over one third of patients (n = 69) had a history of liver abscess, and 16 patients had multiple episodes (range 0-4), resulting in a total of 90 abscess episodes reported in the entire cohort. Multiple concurrent abscesses were common but were counted as a single abscess episode for analysis. Patients with a history of liver abscess had significantly more ALT and ALP elevations than those with no history of abscess ($P < 0.05$). A history of abscess was associated with ALP elevations >5X ULN ($P < 0.05$) and ALT elevations >10X ULN ($P < 0.05$). Microbiological data were available for 27 abscesses. Although Staphylococcus species were the most common organisms identified (17 Staphylococcus aureus, 11 coagulase-negative staphylococci, 7 both), Staphylococcus aureus was found as the unique organism in only 5 cases. Seventeen abscesses were polymicrobial. Six patients had fungal abscesses due to Candida, Aspergillus, and Cryptococcus species. Mycobacterium fortuitum was found in 1 case, as were Nocardia, Burkholdia cepacia, Enterobacter, Enterococcus, pediococcus, lactobacillus and Aerobacter species. Fifty-two of the 69 (75%) patients underwent hepatic resection, while 8 were managed with percutaneous drainage and 9 underwent both procedures. Similar to previous reports, a high rate of surgical complications was encountered, occurring in 34 (49%) patients.[9,12]

After liver abscess, drug-induced hepatotoxicity was the most commonly identified cause of liver enzyme elevation. Enzyme elevation was attributed to medication use if all other etiologies were excluded and improvement was documented with discontinuation of the suspected offending agent or if a typical pattern of hepatotoxicity was noted on liver biopsy. Based on these criteria, a suspicion of drug-induced liver disease was documented in the chart of 29 patients, and 2 patients had total parenteral nutrition–induced cholestasis. Antimicrobial agents were the most commonly implicated medications. Antifungals were the suspected cause in 9 patients (voriconazole 3, itraconazole 5, amphotericin 1), followed by oxacillin in 8, sulfonamides in 4, cephalosporins in 4 and individual cases from cyclosporin A, tacrolimus, levofloxacin, chloramphenicol, and possibly IFN-γ. In numerous cases, more than one possible medication was suspected; however, all agents were stopped simultaneously, making definitive identification of the culprit agent difficult. In 93% (27/29) of cases, drug toxicity caused an ALT elevation: purely hepatocellular in 11 patients (38%), a mixed pattern in 10 patients (35%), and a persistent cholestatic pattern with ALT flares in 6 patients (21%).

Other Abnormalities

In addition to enzyme elevations, other hepatic abnormalities were noted on abdominal imaging, including ultrasound, CT, and magnetic resonance imaging. Of the 165 patients with radiological studies available for review, 56 (34%) had hepatomegaly; 92 (56%) had splenomegaly, including 5 with massive splenomegaly; and 46 (28%) had enlargement of both the liver and spleen. Calcifications were seen in the liver in 41 (25%) patients and in the spleen in 6 (4%) patients. Other findings included retroperitoneal adenopathy in 41 (25%) patients and splenic abscess in 3 (2%) patients. Patients with a previous history of liver abscess were more likely to develop hepatomegaly and/or splenomegaly ($P < 0.05$) and were more likely to have hepatic calcifications on imaging ($P < 0.0001$). Patients with hepatomegaly and/or splenomegaly most commonly had a cholestatic pattern of liver enzyme elevation.

Associations

To evaluate the predictors of the development of splenic and hepatic enlargement, univariate and multivariate logistic regression were performed (Table 2). By univariate analysis, male sex, genotype $gp91^{phox}$, an increasing number of episodes of liver abscess, higher mean ALT as well as increasing number of ALT and ALP elevations were predictive of the development of splenomegaly, while a pattern of normal or near-normal enzymes during follow-up was associated with a decreased risk. Multivariate logistic regression analysis revealed that genotype $gp91^{phox}$ (OR 6.38, 95% CI 3.07 11.9; $P < 0.0001$), an increasing number of liver abscesses (OR 1.93, 95% CI 1.12-3.32; $P = 0.019$), and total ALT elevations (OR 1.13, 95% CI 1.01-1.26; $P = 0.027$) remained predictive, and normal or near-normal enzymes remained protective ($P = 0.048$) for the development of splenomegaly. CGD genotype appeared to play an important role, because 71 (62%) patients with $gp91^{phox}$ had splenic enlargement, compared with only 15 (26%) patients with the $p47^{phox}$ mutation ($P < 0.01$).

In contrast, by univariate analysis, black race, a history of drug hepatotoxicity, more episodes of liver abscess, total ALT and ALP elevations, and a cholestatic pattern of liver injury were associated with hepatomegaly. Multivariate analysis revealed that only black race (OR 7.04, 95% CI 2.47-20.1; $P = 0.03$) and increasing number of ALT elevations (OR 1.21, 95% CI 1.06-1.38; $P < 0.0001$) were associated with liver enlargement (Table 2).

Certain factors were predictive of the pattern of liver enzyme elevation seen over time (Table 3). A cholestatic pattern of injury was associated with increasing episodes of liver abscess (OR 1.59, 95% CI 1.03-2.50; $P = 0.038$) and with CGD genotype. In patients with the $gp91^{phox}$ mutation, a cholestatic pattern was commonly seen (30%) (OR 3.10, 95% CI 1.43-6.72; $P = 0.004$), whereas in those with the $p47^{phox}$ mutation, this pattern was seen in only 5 patients (9%) (OR 0.23, 95% CI 0.085-0.63; $P = 0.004$) ($P < 0.01$) (Table 1). Patients with the $p47^{phox}$ mutation most commonly had a mixed pattern of enzyme elevation. However, increasing patient age was the only factor associated with a mixed pattern (OR 1.11, 95% CI 1.06-1.16; $P = 0.01$) by multivariate analysis (Table 3). Only a history of drug toxicity was independently associated with a hepatocellular pattern (OR 3.59, 95% CI 1.51-8.54; $P = 0.004$). Normal or near normal enzymes were seen most commonly in younger patients, those with a lower body mass

index and in patients with a genotype other than $p47^{phox}$ or $gp91^{phox}$. Not surprisingly, this pattern was much less common in patients with a history of liver abscess, drug hepatotoxocity, hepatomegaly and/or splenomegaly (data not shown). The factors associated with a history of liver abscess were increased age, total ALP elevations (OR 1.29, 95% CI 1.13-1.48; $P = 0.0002$), total ALT elevations (OR 1.10, 95% CI 1.02-1.18; $P = 0.011$), and a mixed enzyme pattern (OR 2.38, 95% CI 1.12-5.05; $P = 0.024$). However, multivariate analysis revealed that only age (OR 1.29 95% CI 1.08-1.56, $P = 0.0006$) and the number of ALP elevations (OR 1.04 95% CI 1.00-1.07, $P = 0.04$) remained significant (Table 2). CGD genotype was not associated with a history of liver abscess.

Histology

A total of 88 liver specimens from 38 patients were available for histological evaluation. Liver tissue was reviewed after hepatic wedge resection in 59 cases, from autopsy specimens in 12 cases, and from diagnostic core needle liver biopsies in 17 cases. Multiple specimens were reviewed from 16 patients (range 2-8 per patient), largely due to the need for multiple hepatic resections at the time of liver abscess. To ensure that findings were reflective of true liver pathology rather than local periabscess phenomena, only tissue from ≥ 2 cm away from the abscess capsule was evaluated. In 19 specimens, there was inadequate uninvolved liver tissue for review.

A variety of pathological changes were identified in the needle and wedge biopsies (Table 4). Some tissue specimens could not be evaluated for all pathological findings and consequently the denominator used for comparisons reflects the number of specimens that had adequate tissue and staining to evaluate the specific finding in question. Portal and/or lobular chronic hepatitis was seen in almost all evaluable specimens (95%). Non-necrotizing granulomata and evidence of liver abscess were also common (75% and 73%, respectively) (Fig. 1).

Inflammatory duct lesions similar to those seen in primary sclerosing cholangitis were seen in 20% (14/70) of samples in 10 different patients. These consisted mainly of narrowing of large ducts accompanied by concentric fibrosis, periductular edema, and lymphocytic inflammation. Rare obliterative scars and copper accumulation were present, but extensive ductopenia was not seen (see Fig. 2). Evidence of acute cholangitis (neutrophils within interlobular bile ducts) was seen in 11/70 (16%) specimens in 9 different patients and was associated with the total number of episodes of liver abscess (OR 3.08, 95% CI 1.13-8.40; $P = 0.028$).

Abnormalities of both the portal and central veins were common (Fig. 1). A portal venopathy consisting of narrowing or complete obliteration of portal veins on Masson-Trichrome staining was present in 57/71 (80%) specimens from 24 patients. In some cases, this was associated with hypertrophy of the vein wall. Portal venopathy was consistent over time in the 10 patients for whom more than one sample was available for review. Similar changes were found in the central veins in 44/70 (63%) samples from 20 patients and again were seen repeatedly in serial samples from individual patients. Portal and central venopathy were correlated ($P = 0.02$), and both were present in 41/70 (59%) biopsy samples from 19 patients. Total episodes of liver abscess and the number of ALP elevations were associated with central venopathy. However, by

multivariate analysis only the total episodes of liver abscess was significant (OR 9.35, 95% CI 1.04-83.3; *P* = 0.046) (Table 5). Splenomegaly was the only independent predictor of portal venopathy (OR 14.67, 95% CI 1.83-117.7; *P* = 0.016).

Nodular regenerative hyperplasia (NRH) was seen in 4 patients, one of whom later died and was confirmed to have NRH on autopsy. Of these, 1 of 4 patients had portal venopathy, and 2 had both central and portal vein changes. Reticulin staining was performed for only 30 specimens from 25 patients. Early changes of NRH may be missed on small biopsy samples, particularly without reticulin staining. Total ALP elevations were associated with NRH on biopsy or at autopsy (OR 1.20, 95% CI 1.00-1.45; *P* =0.045) (Table 5).

Cirrhosis was not found in any patients. Bridging fibrosis was noted in 2 patients,1 with hepatitis C infection and 1 with nonalcoholic steatohepatitis.

Other abnormalities noted in individual biopsy specimens included sepsis-related cholestasis, drug-induced liver injury, hepatic infarction, aspergillosis, and cat-scratch disease. Sinusoidal dilatation was seen in 22 (38.5%) samples.

Among the 12 autopsy specimens, NRH was seen in 6 (50%) cases, and associated venopathy was found in 5 of these: 1 portal, 2 central, 2 portal and central (Fig. 1). In autopsy cases without NRH, portal venopathy was seen in 1, and both central and portal changes were seen in 3 specimens. Two of the autopsy specimens had no significant hepatic pathology.

DISCUSSION

With the marked improvement in prophylaxis and management of infections, patients with CGD are now typically living into adulthood. Although liver abscesses and granulomatous hepatitis have been described, little else is known about hepatic involvement in CGD.[13] A large cohort of well-characterized patients with CGD was reviewed to better describe the clinical, laboratory, and histological manifestations of CGD in the liver.

Liver enzyme abnormalities were very common, occurring on at least one occasion in 73% of patients. Both transient and persistent elevations of ALP occurred, but elevations of aminotransferases were predominantly transient. The elevations seen were significant, reaching at least 5X ULN for ALP in 13% of patients and for ALT in 22% of patients. A cholestatic pattern of injury was slightly more common than hepatocellular or mixed patterns (23% vs. 18% vs. 18%, respectively; P value not significant), and 41% of patients had only mild or no elevations.

Although liver abscess was the most common cause of liver enzyme elevation, this was the etiology in fewer than half (48.5%) of the patients. Drug hepatotoxicity was documented in 29 cases but likely occurred much more frequently. Enzyme abnormalities were attributed to drug-induced liver injury only when all other etiologies were reasonably excluded, when resolution occurred with medication withdrawal, when a diagnosis of suspected drug hepatotoxicity was noted in the chart, or when a pattern

consistent with drug-induced liver injury was seen on a liver biopsy specimen. Most patients with CGD remain on long-term antimicrobial prophylaxis and may receive other courses of therapy for active infections.[10] It is likely that many of the enzyme elevations seen were attributable to one or more medications; however, this could not be ascertained with certainty. It is often difficult to determine a precise cause for liver enzyme elevations, particularly in the setting of systemic infection.[14] Mild enzyme elevations from suspected drug hepatotoxicity do not always prompt discontinuation of potentially life-saving therapy. Although this is certainly reasonable in the acute setting, it is unknown whether continued therapy (for years in some cases) may lead to progressive liver disease. Several patients had significant abnormalities on liver biopsy, including portal and central venopathy as well as NRH, all of which have been associated with drug-induced liver injury in previous reports[14,15] but not described previously in CGD.[13] Although such changes may be the consequence of repeated hepatic and systemic infections, clarifying the role of chronic drug hepatotoxicity will have important implications for the management of CGD and other chronic diseases.

In addition to liver enzyme elevations, many patients had hepatic and/or splenic enlargement. Although hepatosplenomegaly could result from causes other than chronic liver disease, it is notable that both lesions were associated with more frequent episodes of liver abscess and liver enzyme elevations. In addition, the patients with normal or near-normal liver tests throughout follow-up were unlikely to develop either hepatomegaly or splenomegaly. Liver enlargement was associated with a cholestatic pattern of liver injury. Although ALP elevation is typically associated with cholestasis and biliary abnormalities, it may also be seen with hepatic infiltration or distortion of hepatic architecture.[16] Hepatomegaly and ALP elevation are common in the setting of hepatic infection, particularly by fungal or mycobacterial organisms.[16,17] Repeated liver abscesses as well as hepatic resections may significantly alter hepatic architecture, potentially resulting in ALP elevation, hepatomegaly and/or splenomegaly, and histological changes.

In addition to the previously described granulomata, abscesses, and portal and lobular hepatitis, some novel pathological lesions were seen.[13] Significant abnormalities of the portal or central veins were found in over 80% of the biopsy specimens examined. In addition, NRH was noted in half of the autopsies and over 23% of the biopsy specimens evaluated. Although the pathogenesis is incompletely understood, NRH is a cause of noncirrhotic portal hypertension postulated to result from a primary vasculopathy and obliteration of small portal branches.[18-20] The diagnosis is frequently overlooked due to slow evolution, lack of impairment of hepatic synthetic function, and the need for special staining.[21] Increased resistance to blood flow within the hepatic sinusoids results in portal hypertensive changes.[22,23] It is possible that the vascular changes identified in a high proportion of biopsies may progress, ultimately leading to the development of NRH.

The cause of the vascular abnormalities is unclear. Recurrent liver abscesses and resections may alter the hepatic architecture and lead to changes in both liver inflow and outflow with potential consequences to small portal and hepatic venules over time. Alternatively, granulomata may alter hepatic architecture and lead to NRH, a phenomenon that has been postulated to occur in primary biliary cirrhosis.[24,25] Notably, central venopathy was associated with the number of episodes of liver abscess and portal venopathy was independently associated with splenomegaly. Medications have

also been described to cause both vasculopathy and NRH. Consequently, the etiology may be multifactorial.[26]

The main limitation of this study is its retrospective nature. This limits findings to associative rather than causative. In addition, the cohort may reflect patients with more severe CGD as all included patients were referred to the NIH for evaluation.

In conclusion, liver enzyme elevations are common in patients with CGD, associated primarily with liver abscesses and drug hepatotoxicity. Over time, many patients develop hepatomegaly and/or splenomegaly, which correlate with episodes of liver abscess and frequency of liver enzyme elevation. Hepatic pathology includes granulomata and abscesses, but vascular abnormalities including NRH are also common. Whether vasculopathy results from repeated liver abscesses, drug hepatotoxicity, or other processes is currently unknown. As patients with CGD continue to live longer, understanding the consequences of hepatic pathology will become more important. In addition, CGD may serve as a model to evaluate the progression from vasculopathy to NRH.

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Abbreviations: ALP, alkaline phosphatase; CGD, chronic granulomatous disease; NRH, nodular regenerative hyperplasia; ULN, upper limit of normal.

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Table 1. Patient Characteristics by CGD Genotype

	Total	gp91^{phox}	gp47^{phox}	gp22^{phox}	gp67^{phox}	Unknown Genotype
Number (n)	194	114	56	4	3	17
Age (yr)	19.5 ± 10.8	17.7 ± 8.6*	23.9 ± 12.4*,†	26.2 ± 13.3	26.0 ± 18.8	13.9 ± 10.8†
Sex (M/F)	150/44 (77.3/22.7)	106/8* (93.0/7.0)	25/31*,† (44.6/55/4)	3/1 (75/25)	2/1 (66.6/33.3)	14/3† (82.4/17.6)
Body mass index‡	20.9 ± 5.9	20.2 ± 6.0	23.0 ± 5.5*	21.6 ± 1.3	22.4 ± 10.9	16.8 ± 2.3*
Ethnicity						
Caucasian	155 (80.0)	94 (82.5)	43 (76.8)	3 (75)	2 (66.6)	13 (76.5)
African American	22 (11.3)	12 (10.5)	10 (17.9)	0	0	0
Hispanic	12 (6.2)	5 (4.4)	3 (5.5)	1 (25)	1 (33.3)	2 (11.8)
Asian	5 (2.6)	3 (2.6)	0	0	0	2 (11.8)
ALT (mean IU)§	32.9 ± 35.6	31.6 ± 27.6	37.9 ± 51.5	40.7 ± 18.8	43.7 ± 45.3	21.1 ± 8.2
AST (mean IU)	35.5 ± 35.4	33.9 ± 20.8	41.3 ± 58.2	34.7 ± 9.7	32.9 ± 20.0	28.9 ± 10.8
ALP (mean IU)	191.3 ± 132	182.2 ± 89.5	208.9 ± 200	132.6 ± 24.8	312.4 ± 200	188.5 ± 63.3
Bilirubin (mean mg/dl)	0.56 ± 0.86	0.45 ± 0.23	0.61 ± 1.12	0.48 ± 0.20	0.78 ± 0.86	0.37 ± 0.15
Total number of ALP elevations‖	1.7 ± 3.2	1.7 ± 2.8*	1.5 ± 2.5†	9.5 ± 11.5*,†	3.6 ± 4.7	0.45 ± 0.5
1-2×	0.93 ± 2.3	0.75 ± 1.5	0.82 ± 1.6	8.75 ± 10.8	3.0 ± 4.4	0.35 ± 0.5
2-5×	0.57 ± 1.6	0.66 ± 1.8	0.54 ± 1.4	0.5 ± 0.6	0.33 ± 0.6	0.12 ± 0.3
5-10×	0.15 ± 0.7	0.20 ± 0.8	0.13 ± 0.7	0	0	0
>10×	0.06 ± 0.4	0.08 ± 0.5	0.02 ± 0.1	0.25 ± 0.5	0.33 ± 0.6	0
Persistent ALP elevation	49 (25.3)	38 (33.3)*	10 (17.9)*	1 (25)	0	0
Total number of ALT elevations‖	2.8 ± 4.3	2.9 ± 4.4†	2.8 ± 4.0*	11 ± 7.7*,†	3.3 ± 2.5	0.29 ± 0.7
1-2×	1.64 ± 2.5	1.63 ± 2.2	1.73 ± 2.8	6.75 ± 5.6	1.0 ± 1.0	0.29 ± 0.7
2-5×	0.73 ± 1.5	0.75 ± 1.5	0.75 ± 1.5	3.0 ± 3.6	0.33 ± 0.6	0
5-10×	0.30 ± 0.8	0.35 ± 0.9	0.20 ± 0.4	0.75 ± 0.5	1.67 ± 2.9	0
>10×	0.15 ± 0.4	0.15 ± 0.4	0.16 ± 0.4	0.5 ± 0.6	0.33 ± 0.6	0
Persistent ALT elevation	4 (2.1)	0	3 (5.4)	0	1 (33.3)	0
History of abscess	69 (34)	39 (34.2)	19 (33.9)	3 (75)	3 (100)	5 (29.4)
Abscess episodes	0.47 ± 0.7	0.44 ± 0.7	0.46 ± 0.8	1.3 ± 1.0	1.3 ± 0.6	0.3 ± 0.5
Hepatotoxicity	29 (14.9)	15 (13.2)	11 (19.6)	2 (50)	1 (33.3)	0
Hepatomegaly	56 (34)	38 (33.3)	14 (25)	2 (50)	0	2 (11.7)
Splenomegaly	92 (56)	71 (62.2)*	15 (26.8)*	2 (50)	2 (66.6)	2 (11.7)
Enzyme pattern						
Cholestatic persistent	24 (12.4)	21 (18.4)*	2 (3.6)*	1 (25)	0	0
Cholestatic acute	7 (3.8)	3 (2.6)	0	0	0	4 (23.5)
Cholestatic + flares	14 (7.3)	11 (9.6)	3 (5.4)	0	0	0
Hepatocellular	35 (18)	21 (18.4)	12 (21.4)	1 (25)	1 (33.3)	0
Mixed	35 (18)	16 (14.0)*	16 (28.6)*	2 (50)	1 (33.3)	0
Normal/Near-normal	79 (40.7)	42 (36.8)	23 (41.1)	0	1 (33.3)	13 (76.5)

*,†$P < 0.05$ for comparison between indicated groups by ANOVA.

‡Mean ± SD.

§Mean values for ALT, AST, ALP, and bilirubin indicate the mean value during the entire length of follow-up.

‖Values refer to transient ALP or ALT elevations to value × ULN.

Table 2. Univariate and Multivariate Logistic Regression Demonstrating Predictors of Hepatomegaly, Splenomegaly, and Liver Abscess

Factor	**OR* (95% CI)**	**Univariate *P* Value**	**Multivariate *P* Value**
Splenomegaly			
Genotype gp91	6.38 (3.07-11.9)	<0.0001	<0.0001
No. of abscess episodes	1.93 (1.12-3.32)	0.0045	0.019
No. of ALT elevations	1.13 (1.01-1.26)	0.0005	0.027
Normal enzyme pattern	0.29 (0.16-0.54)	<0.0001	0.049
Female versus male sex	0.32 (0.18-0.78)	0.0081	NS
History of abscess	2.13 (1.17-3.87)	0.0136	NS
Mean ALT	1.02 (1.01-1.04)	0.0094	NS
Genotype gp47	0.47 (0.22-0.99)	0.0004	NS
No. of ALP elevations	1.18 (1.05-1.33)	0.0068	NS
Persistent ALP elevation	2.37 (1.22-4.63)	0.011	NS
Hepatomegaly			
Black vs. Caucasian	7.04 (2.47-20.1)	0.005	0.03
No. of ALT elevations	1.21 (1.06-1.38)	<0.0001	<0.0001
Drug hepatotoxicity	3.24 (1.44-7.28)	0.0044	NS
No. of abscess episodes	1.83 (1.20-2.72)	0.0048	NS
No. of ALP elevations	1.28 (1.13-1.45)	0.0001	NS
Persistent ALP elevation	2.66 (1.35-5.26)	0.0049	NS
Cholestatic pattern	2.21 (1.10-4.45)	0.026	NS
Liver abscess			
Age (yr)	1.05 (1.02-1.09)	0.0005	0.029
No. of ALP elevations	1.29 (1.13-1.48)	0.0002	0.003
No. of ALT elevations	1.10 (1.02-1.18)	0.011	NS
Mixed enzyme pattern	2.38 (1.12-5.05)	0.024	NS

Abbreviation: NS, not significant.
*For factors significant by multivariate regression, odds ratios indicated multivariate OR, for other factors, odds ratios are from univariate logistic regression.

Table 3. Univariate and Multivariate Logistic Regression Demonstrating Associations with Pattern of Liver Enzyme Elevation

Factor	**OR* (95% CI)**	**Univariate *P* Value**	**Multivariate *P* Value**
Cholestatic**			
No. of abscess episodes	1.59 (1.03-2.50)	0.04	0.038
Hepatomegaly	2.21 (1.10-4.45)	0.026	NS
Genotype gp91	3.10 (1.43-6.72)	0.004	NS
Genotype gp47	0.23 (0.05-0.63)	0.005	0.004
Hepatocellular			
Drug hepatotoxicity	3.59 (1.51-8.54)	0.004	0.004
Mixed			
Age	1.11 (1.07-1.16)	<0.0001	<0.0001
Drug hepatotoxicity	3.09 (1.28-7.45)	0.012	NS
History of abscess	2.40 (1.14-5.10)	0.022	NS
No. of abscess episodes	1.66 (1.07-2.57)	0.025	NS
Genotype gp47	2.29 (1.07-4.92)	0.033	NS
Normal/Near-normal			
Age	0.92 (0.89-0.96)	<0.0001	0.009
Duration of follow-up	0.94 (0.90-0.99)	<0.0001	<0.0001
Body mass index	0.89 (0.82-0.96)	0.003	NS
Genotype gp91	0.23 (0.08-0.71)	0.008	NS
Genotype gp47	0.25 (0.08-0.89)	0.008	NS

*For factors significant by multivariate regression, odds ratios indicated multivariate OR, for other factors, odds ratios are from univariate logistic regression.
**All cholestatic patterns (transient, persistent, and cholestatic with ALT flares) were grouped together for logistic regression analysis.

Table 4. Histological Findings in the Liver		
	Pathology Specimens	**Number of Patients**
Number	88	38
Specimens/patient	NA	2.3 (0-8)
Specimen type		
Needle	17 (19.3)*	15
Wedge	59 (67.0)	22
Autopsy	12 (13.6)	12
Lobular/Portal hepatitis	67/71 (94.4)	29/31 (93.5)
Abscess	55/76 (72.4)	23/30 (76.7)
Granulomata	56/75 (74.7)	23/31 (74.2)
Duct lesions	14/70 (20.0)	10/31 (32.3)
Acute cholangitis	11/70 (15.7)	9/29 (31.0)
Vasculopathy	60/71 (84.5)	25/31 (80.6)
Central	44/70 (62.9)	20/30 (66.7)
Portal	57/71 (80.3)	24/31 (77.4)
Both	41/70 (57.1)	19/30 (63.3)
NRH	10/42 (23.8)†	9/29 (31.0)
Cirrhosis/Bridging fibrosis	2/27 (7.4)‡	2/19 (10.5)

*Percentage of those specimens with each specific finding as a proportion of those with adequate tissue for evaluation.
†Specimens for which reticulin staining was performed (30 biopsies, 12 autopsies).
‡Specimens for which Masson trichrome staining was performed.

Table 5. Univariate and Multivariate Logistic Regression Demonstrating Associations with Biopsy Findings

Factor	**OR (95% CI)**	**Univariate *P* Value**	**Multivariate *P* Value**
Central venopathy			
No. of abscess episodes	9.35 (1.04–83.3)	0.033	0.045
No. of ALP elevations	1.45 (1.00–2.11)	0.049	NS
Portal venopathy			
Splenomegaly	14.67 (1.83–117.7)	0.016	0.016
Acute cholangitis			
No. of abscess episodes	3.07 (1.13–8.40)	0.028	0.028
NRH			
No. of ALP elevations	1.20 (1.00–1.45)	0.045	0.045

Abbreviation: NS, not significant.

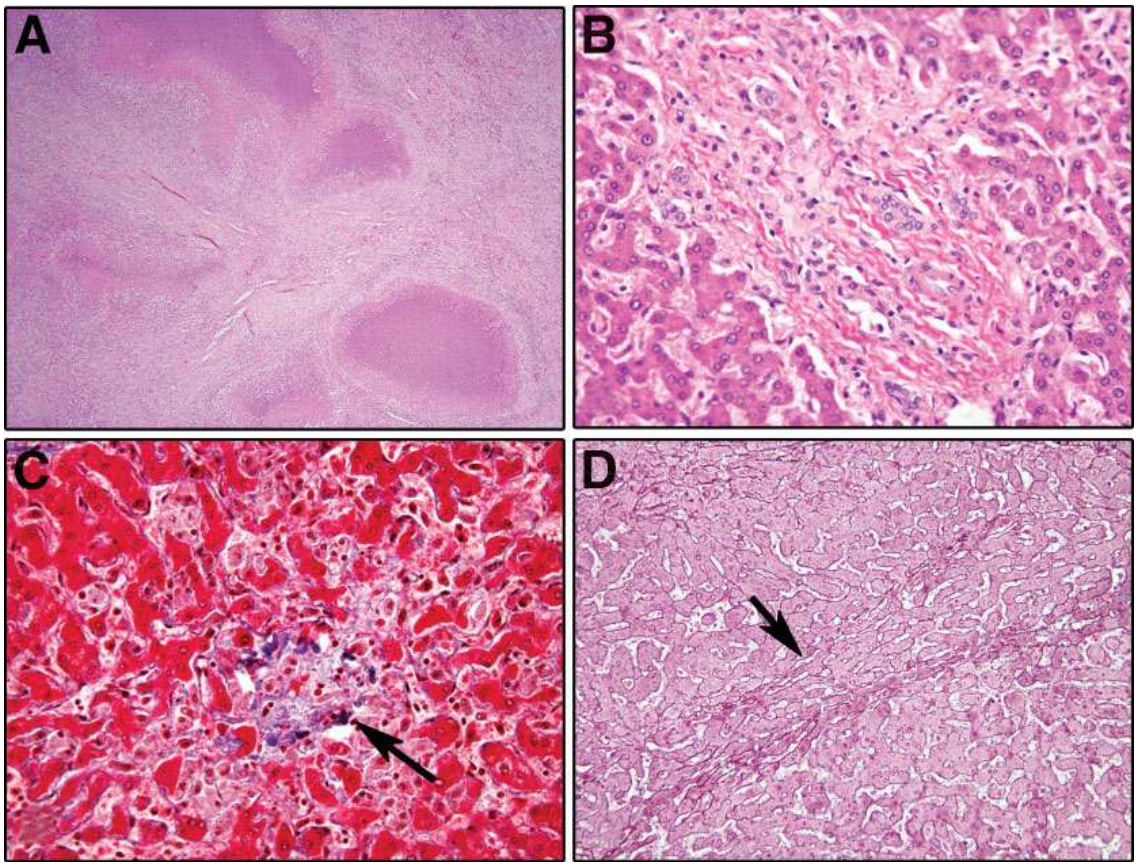

Figure 1. Hepatic pathology in CGD. (A) Multiloculated abscesses are present within dense fibroinflammatory connective tissue. The abscesses are irregular in outline and are surrounded by a thin cuff of epithelioid macrophages. The connective tissue around the abscesses contains remnants of portal areas, lymphocytes, eosinophils, and pigmented macrophages (hematoxylin-eosin stain). (Original magnification X40.) (B) Portal area showing obliteration of the normal portal vein. Small slit-like vessels may be seen along with the normal artery and vein. Only minimal inflammation is present, but pigmented macrophages are seen in the center of the portal area (hematoxylin-eosin stain). (Original magnification X400.) (C) A small central vein lumen is obliterated by loose connective tissue. Only the collagenous vein wall (arrow) remains as a marker of the vein's location. The surrounding sinuses are dilated and filled with pigmented macrophages (Masson trichrome stain). (Original magnification X400.) (D) Some of the specimens showed evidence of nodular regenerative hyperplasia. In this field, cords of narrowed, atrophic hepatocytes (arrow) are seen sandwiched between hypertrophic, widened liver cell plates (reticulin stain). (Original magnification X200.)

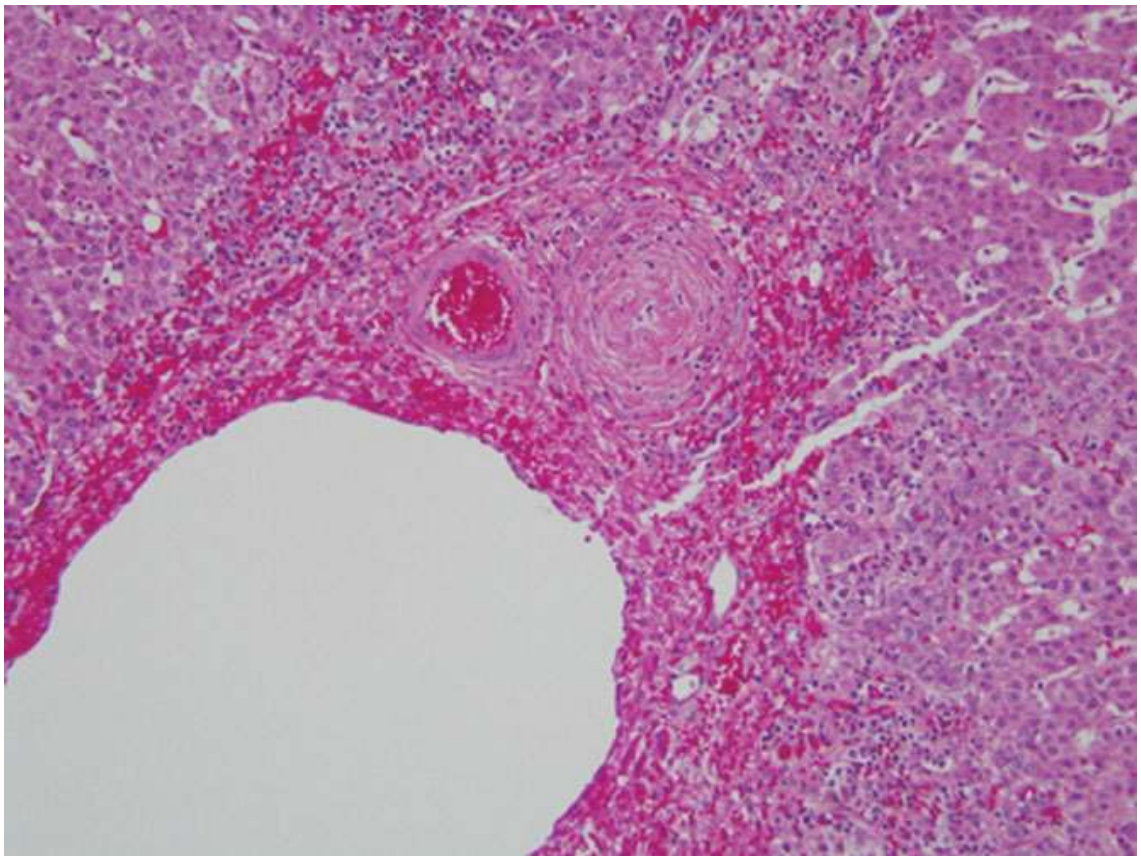

Figure 2. Obliterative duct lesion. A representative portal area from a hepatic resection specimen at a site distant from abscesses. The duct is obliterated and replaced by a concentric scar approximately the same size as the artery. The portal area also shows hemorrhage and mild peripheral chronic inflammation (hematoxylin-eosin stain; original magnification X100).