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Letter to the Editor

CLL associated giant cell hepatitis

Giant cell hepatitis is a common pathological finding in infants with hepatic failure, however, it is exceedingly rare in adults. The estimated prevalence of post infantile giant cell hepatitis (PIGCH) is 0.1–0.25% with no age or gender preponderance [1]. It is a nonspecific form of hepatitis and a wide range of etiologies have been implicated or associated as the cause. The most common association is autoimmune liver disease which accounts for approximately 40% of published cases [1]. Other etiologies described include medications, viral infections, autoimmune diseases and CLL (Table 1) [1,2]. PIGCH is defined histologically by syncytial giant cell transformation of the hepatocytes. It is postulated to be a non-specific reaction to various stimuli from etiologies mentioned above leading to the formation of a syncytium with failure of cytoplasmic division in sync with nuclear division during brisk regeneration in response to hepatocellular necrosis [3]. We present a patient who presented with PIGCH in the setting of newly diagnosed chronic lymphocytic leukemia (CLL) with significant lymph node and parenchymal organ involvement.

A 52-year-old man with no known past medical problems presented to the hospital with four days of jaundice, nausea, night sweats, exhaustion and 25-pound weight loss over 4–5 months. At presentation, he was afebrile, with stable hemodynamic parameters. His physical exam was remarkable for prominent scleral icterus, firm non-tender diffuse lymphadenopathy involving the neck, axillary and inguinal regions without clinical hepatosplenomegaly. Laboratory evaluation revealed hemoglobin 11.8 g/dL (13.0–18.0 g/dL), white blood cell count 18/uL (3.8–10.6 10*3/uL), absolute lymphocyte count 12/uL (0.7–4.5 10*3/uL), platelet count 175/uL (150–440 10*3/uL), alanine transaminase (ALT) 1164 U/L (8–39 U/L), aspartate transaminase (AST) 1210 U/L (17–35 U/L), total bilirubin 27.7 mg/dL (0.1–1.2 mg/dL), direct bilirubin 19 mg/dL (0.0 - 0.5 mg/dL), prothrombin time (INR) 22.2 secs (2.0) [9.4–12.5 seconds (ratio)], alkaline phosphatase 148 U/L (39–113 U/L). Computed tomography (CT) of the abdomen and pelvis showed splenomegaly and bulky adenopathy within the upper and lower abdomen particularly involving the porta hepatis and precaval regions. The gallbladder and biliary ductal systems were unremarkable. Peripheral blood flow cytometry analysis confirmed a monoclonal B-cell population (CD20+/CD5+/CD10-/CD23+/Kappa+) with a composite immunophenotype characteristic of chronic lymphocytic leukemia (CLL). An excisional biopsy of right inguinal lymph node showed diffuse proliferation of small lymphocytes associated with numerous proliferating centers consistent with CLL.

His liver enzymes and bilirubin continued to worsen with a peak AST of 1727 U/L, ALT of 1672 U/L, and total bilirubin of 46.3 mg/dL (direct bilirubin 28.2 mg/dL). Further evaluation for the etiology of hepatitis revealed a negative acetaminophen level, acute hepatitis panel, and human immunodeficiency virus. Epstein Barr viral serology (Positive IgG and negative IgM) was indicative of past infection. Serology for CMV IgM and IgG were strongly positive. However, CMV DNA PCR resulted negative (< 390 viral copies/mL). Ceruloplasmin and alpha-1-antitrypsin levels were normal. ANA (antinuclear antibody) was positive 1:160 with speckled pattern along with positive F-actin smooth muscle IgG antibody; however anti-smooth muscle antibody and anti-mitochondrial (M2) antibody resulted negative. He had a macrocytic anemia and workup for hemolysis showed normal B12, folate, haptoglobin, lactate dehydrogenase (LDH). Red blood cell (RBC) morphology showed no schistocytes. Liver biopsy showed severe diffuse as well as focal tumoral involvement of liver parenchyma and portal area tracts with abnormal lymphocytes (Fig. 1A–E). In addition, the biopsy was consistent with acute giant cell hepatitis in association to submassive hepatic necrosis (Fig. 1B, 1C). He was started on prednisone 100 mg daily to treat the giant cell hepatitis and subsequently had significant clinical and biochemical improvement with a steady decline in liver enzymes with AST/ALT to 325/650 U/L respectively while inpatient. He was discharged on prednisone 40 mg daily which was tapered over the next two months. At the time of steroid discontinuation, evaluation of his liver enzymes revealed AST of 46 U/L, ALT of 56 U/L and total bilirubin of 0.9 mg/dL. In subsequent follow up one month after stopping prednisone he had complete resolution of liver enzyme abnormalities with AST 21 U/L, ALT 24 U/L and total bilirubin of 0.7 mg/dL.

As discussed above, GCH is a rare disorder in adults and our literature search identified a little over 100 cases of GCH reported in the last 20 years, of which four cases were described in association with CLL [1–4]. The uniqueness of our case is the liver involvement of CLL and acute liver failure due to PIGCH. CLL is a slow, progressive disorder of abnormal and malignant neoplastic B lymphocytes and generally follows an indolent course [5]. It is estimated to account for 19,000 new cases every year in the United States [5]. Clinical presentation varies from an asymptomatic disease in a majority of patients to a symptomatic disease requiring treatment [6]. Liver dysfunction in patients with CLL predicts an overall poor outcome [7]. Although liver dysfunction and CLL involvement in the liver are frequently reported, CLL causing acute liver failure is extremely rare [8]. Gupta E et al [9] described a case of PIGCH in the setting of CLL in a patient who received chemotherapy and had hypogammaglobulinemia. These associated factors were postulated to have increased the risk of liver failure in this patient. Our patient had no exposure to chemotherapy and had normal quantitative immunoglobulins levels. Gupta N et al [3] describes a case of GCH similar to our patient in the setting of CLL after careful exclusion of other associations such as infection, autoimmunity, and medications.

Patients with CLL are susceptible to viral infections due to altered cell-mediated immunity [2]. Our patient had positive IgM and IgG serologies for CMV. We opted against antiviral treatment given the negative CMV DNA by PCR and excellent clinical improvement to corticosteroids. It is unlikely that our patient's positive CMV serology contributed to GCH given the response to steroids and lack of other findings suggestive of acute CMV infection. Several other viral

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Table 1
Clinical disorders associated with giant cell hepatitis.

Infections	Human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, Paramyxovirus, hepatitis A, hepatitis B, hepatitis C, hepatitis E.
Autoimmune diseases	Autoimmune hepatitis, primary sclerosing cholangitis, polyarteritis nodosa, ulcerative colitis
Medications	Amoxicillin- clavulanic acid, doxycycline, aminosalicylic acid, 6-mercaptopurine, methotrexate, vinyl chloride, amitriptyline, chlordiazepoxide, chlorpromazine, clometacin and and herbal supplements
Hematological disorders	Autoimmune hemolytic anemia, Chronic lymphocytic leukemia, hypereosinophilia, sickle cell disease, hereditary spherocytosis
Granulomatous diseases	Sarcoidosis, necrobiotic xanthogranuloma

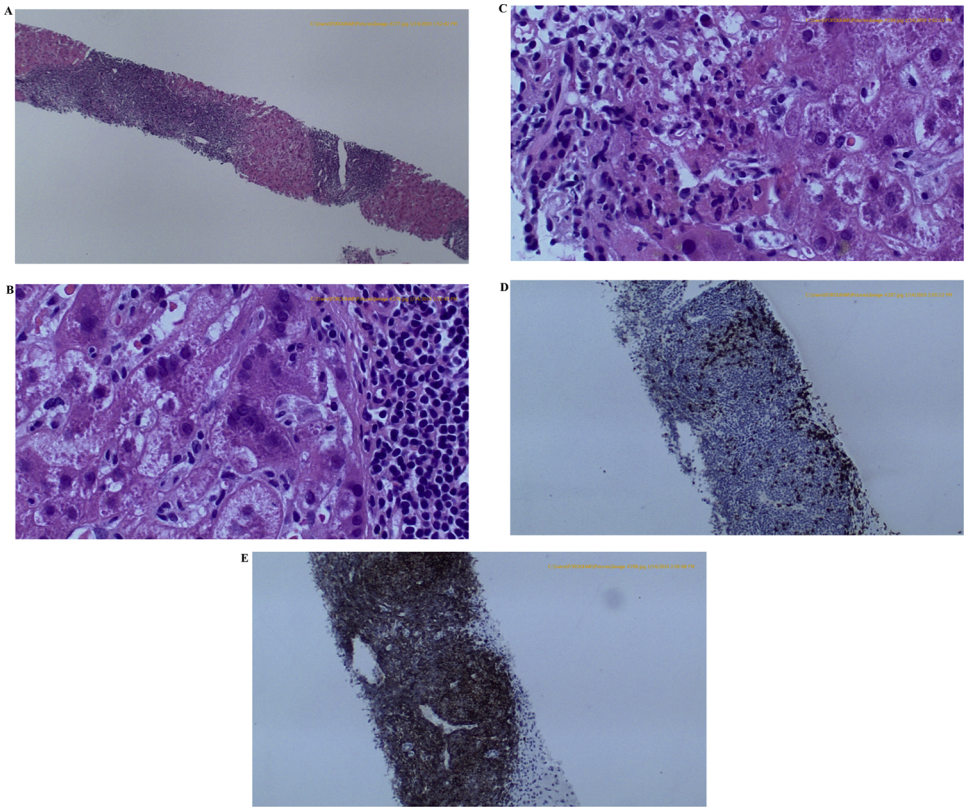

Fig. 1. (A) H&E, x40: Expansive nodular infiltration of portal areas by small Well Differentiated Lymphoma (WDL) lymphocytes. (B) H&E, x 400: The interface between portal area and liver parenchyma demonstrates syncytial giant cell formation of hepatocytes hence the term Giant Cell Hepatitis. A few lymphoma/leukemia cells are noted in the sinusoids. Note: small WDL lymphocytes in the portal area and the liver parenchyma. (C) H&R, x400: The interface zone show focal (center of the field) confluent necrosis of hepatocytes with fibrin deposition and neutrophilic infiltration. This is characteristic of sub-massive hepatic necrosis and explains patient's liver profile and related clinical findings. (D) CD3 immunoperoxidase stain, x100: Scanty, scattered T cells pattern of the lymphocytic infiltration of portal area. (E) CD20 immunoperoxidase stain, x100: Prominent, diffuse B cell nature of lymphocytic "lymphoma" infiltration of portal area.

infections have been reported as an association to PIGCH. Hepatitis C is the most commonly implicated viral organism, accounting for approximately 42% of reported viral PIGCH cases [10,11]. Other viral organisms which have been reported to be associated include HAV, HBV, HEV, CMV, EBV, HIV, HHV6a and unidentified paramyxo-like virus. The probable pathogenesis is a non-specific reaction of immune system activation to viral particles in the infected hepatocytes leading to the morphological cellular changes [12]. In a review by Phillips et al [13], eight of ten patients with GCH had particles that resembled nucleocapsids of paramyxovirus with budding of viral particles from the cellular membrane when examined under electron microscopy. In a review by Bihari et al [1], two cases of PIGCH in patients with CLL had paramyxovirus-like particles on electron microscopy [9,14].

Autoimmune hepatitis, mainly type 1, or ANA positivity accounts for 40% of all autoimmune related GCH. The underlying mechanism is unclear but is hypothesized to be from a fusion of mononuclear hepatocytes or nuclear proliferation that is not followed by cellular division [15]. Our patient had positive ANA and F-actin antibody, but autoimmune hepatitis is unlikely the cause as anti-smooth muscle and antimitochondrial M2 antibodies were negative. Several medications have been reported to be associated with GCH and they include but are not limited to methotrexate, 6-mercaptopurine, p-aminosalicyclic acid, vinyl chloride, chlorpromazine, ISABGOL, clometacine, augmentin, and doxycycline. Herbal medications causing GCH have been reported in case reports [16]. The likely mechanism is the direct injury of hepatocytes from these medications. Our patient had not taken any medications or herbal supplements prior to hospital admission.

There are no clear guidelines in regards to management of GCH, and treatment as of now is unclear. Determining the underlying etiology is an important step, as there have been various treatments proposed based on the underlying cause. In cases of PIGCH due to autoimmune causes or CLL, immunosuppressive therapy has had moderate success. Tajiri et al [17] reported a case of PIGCH due to autoimmune hepatitis treated successfully with corticosteroids and subsequent low dose azathioprine. Gupta N et al [3] reported initial improvement after high dose prednisone and maintenance therapy with rituximab given relapse of disease in a patient with PIGCH and CLL. Philips et al [13] reported ten cases of GCH in children and adults thought to be due to viral or autoimmune etiology who were treated with prednisone or supportive care. Of this group, none responded to steroid therapy, 50% required orthotic liver transplantation, and the remaining 50% did not survive. As mentioned above these patients had paramyxovirus-like particles in the multinucleated giant cell hepatocytes. This yet unidentified virus has some relationship with paramyxoviridae and is morphologically similar to measles nucleocapsid particles [13]. There are some limited case reports where paramyxovirus associated cases were treated with ribavirin, although further research to determine its utility is required [18]. Other treatments reported were intravenous immunoglobulin, rituximab and liver transplantation.

In summary, we reported a case of PIGCH in a patient with newly

diagnosed CLL who had a dramatic improvement in liver function after initiation of high dose steroid therapy. CLL as an association or predisposing factor to GCH is rare, with only four cases reported to date. Our case demonstrates that prompt initiation of high dose steroid therapy can be successful in the recovery of liver function and prevent the need for transplantation. Our patient recovered completely after initial high dose prednisone therapy followed by slow taper over a two month period of time and has not needed additional immunosuppressive therapy or treatment for CLL to date. Frequent follow up of these patients is necessary as other cases have shown relapse requiring further immunosuppressive agents. Patients with features of GCH on biopsy should have an extensive workup to identify the causes discussed above and if not contraindicated, prompt initiation of systemic corticosteroids can be life-saving. Given the limited data and unclear guidelines there is a need for further studies to establish clear guidelines for the approach and use of therapeutic regimens to treat a mysterious, underreported disease entity.

Declarations of interest

None.

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