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Syncytial giant cell hepatitis in a patient with chronic lymphocytic leukemia

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Abstract

While it commonly occurs in the pediatric population, syncytial giant cell hepatitis is rare in adults, which is diagnosed histologically by the presence of multinucleated cells in the liver. The literature has recorded only approximately one hundred cases in adults during the past two decades in whom malignancy is rarely associated with giant cell hepatitis. Our patient is a 66-year-old woman who was diagnosed with chronic lymphocytic leukemia (CLL) and subsequently developed syncytial giant cell hepatitis. This disease is usually linked to virus infection, autoimmune diseases, and drug medications. The association between CLL and giant cell hepatitis is rare, with only three cases reported. In most cases viral particles on electron microscopy are reported and the patients usually have a history of chemotherapy and hypogammaglobulinemia. Unlike such cases, our patient developed giant cell hepatitis in the absence of such confounding variables. The treatment for our patient was a high-dose corticosteroid and rituxan, with improvement in liver enzymes.

Keywords

chronic lymphocytic leukemia; giant cell hepatitis; postinfantile giant cell hepatitis; syncytial giant cell hepatitis

INTRODUCTION

Syncytial giant cell hepatitis, commonly occurs in the pediatric population, is a rare disorder in adults that is diagnosed histologically by the presence of multinucleated cells in the liver.¹ Only approximately one hundred cases in adults have been recorded in the literature for the past two decades.¹ The etiologies of giant cell hepatitis vary among the individuals, including medications such as methotrexate, amitriptyline, herbal medicines and doxycycline,^{2,3} autoimmune disorders such as autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis and primary sclerosing cholangitis,^{4,5} as well as the infection with viruses such as hepatitis A, B, C and E viruses, Epstein–Barr virus (EBV), human immunodeficiency virus (HIV), cytomegalovirus (CMV) and paramyxovirus.^{6,7} Malignancy has been rarely associated with giant cell hepatitis, and only three cases of giant cell hepatitis have been reported to be related to chronic lymphocytic leukemia (CLL).^{8–10}

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The presentations of syncytial giant cell hepatitis range from acute hepatitis and mild chronic liver disease to rapid progression of cirrhosis.¹¹ Here we reported a case of 66-year-old Caucasian woman who was diagnosed with CLL and subsequently developed syncytial giant cell hepatitis.

CASE REPORT

A 66-year-old Caucasian woman with a medical history of hypertension and hyperlipidemia was diagnosed with Rai stage I CLL. In June 2013 routine lab examination, while asymptomatic, revealed a lymphocyte-predominant leukocytosis with a white blood cell (WBC) count of $21.3 \times 10^9/L$ (71% lymphocytes) but otherwise stable parameters (hemoglobin 143g/L, hematocrit 42.5% and platelet count $177 \times 10^9/L$). A peripheral blood smear showed most of the cells were small lymphocytes, and peripheral blood flow cytometry showed that 80% of lymphocytes in the blood were CD19⁺, CD20dim⁺, CD5⁺, CD23⁺, CD10⁻, CD43⁺, FMC7⁻, CD11c⁻, immunoglobulin M (IgM) dim⁺, low density lambda restricted monoclonal B cells consistent with the diagnosis of CLL. Cytogenetics using fluorescence *in situ* hybridization (FISH) showed del 17p, del 13q and del 11q22 with del 17p and del 11q, placing her in the poor prognostic group. HIV, hepatitis B or C virus infection were negative. Since she was relatively asymptomatic, she was monitored as an outpatient with no treatment interventions.

In middle of June 2014, her WBC count rose to $65.2 \times 10^9/L$, and uric acid was elevated to 9.1mg/dL. She was started on allopurinol on 24 June 2014 but developed epigastric pain after the administration of the drug, so allopurinol was discontinued on 5 July. Following the discontinuation of allopurinol, her liver enzymes began to rise (Table 1). From 7 to 14 July, her alanine transaminase (ALT) rose from 237U/L to 1950U/L and aspartate transaminase (AST) from 159U/L to 1770 U/L. On 22 July her liver enzymes peaked with AST and ALT reached 3480U/L and 4240U/L, respectively, and her WBC count rose to $101 \times 10^9/L$ with 96% lymphocytes.

Her work-up consisted of computed tomography (CT) of abdomen and pelvis, showing marked diffuse adenopathy and splenomegaly but was negative for any thrombosis. Hepatitis A, B and C viruses, EBV, CMV, human herpes virus 6, herpes simplex virus (HSV) and autoimmune work-up, including antimitochondrial, anti-smooth, anti-nuclear and anti-LKM1 antibodies, were all negative. Deep fluorescent antibody and polymerase chain reaction (PCR) for respiratory syncytial virus influenza A/B, parainfluenza 1–3 and adenovirus were also negative, and a right upper quadrant ultrasound was negative for Budd–Chiari syndrome and portal vein thrombosis. She had no evidence of hypogammaglobulinemia with normal IgG, IgM, and IgA levels. She had no history of alcohol abuse, illicit drug use, blood transfusion or any other prior liver disease. The work-up of her CLL was repeated, including a peripheral blood smear showing multiple smudge cells and mature lymphocytes and flow cytometry demonstrating that 90% of the blood cells were consistent with the known CLL.

On 23 July liver biopsy was performed, which showed portal tracts distended by monomorphic lymphocytes that were positive for PAX5 and CD5 and liver parenchyma with

extensive giant cell transformation of hepatocytes. Electron microscopy showed distorted hepatocytes with cytoplasmic proteinaceous vacuoles, dilated mitochondria, and abundant glycogen granules but in the absence of viral particles. Her giant cell transformation was attributed to allopurinol, which had already been stopped. She completed oral N-acetylcysteine treatment and was started on prednisone 60mg since she had become increasingly jaundiced and her total bilirubin had risen to 17.7mg/dL (direct bilirubin 13.2mg/dL).

After this episode of acute hepatitis, her leukocytosis continued to rise, with an increase to $135 \times 10^9/L$ in August 2014, although confounded by the initiation of steroids. A blood smear showed no hemolysis, and peripheral blood cytometry showed 90% monoclonal B cells, which was consistent with CLL. Positron emission tomography (PET)-CT showed lymphadenopathy and splenomegaly consistent with CLL. Over the next months, her liver enzymes normalized, therefore prednisone was slowly tapered to 15mg.

On 1 December 2014 her ALT and AST rose to 1100U/L and 626U/L, respectively, with a stable WBC count of $51.6 \times 10^9/L$. On 4 December her AST and ALT levels were even increased to 1120U/L and 2390 U/L, respectively (Table 1). At that time, she was no longer on allopurinol, and a work-up including hepatitis panel, PCR for EBV, CMV and adenovirus, anti-nuclear antibodies and anti-smooth muscle antibody were negative. Repeated liver biopsy on 8 December revealed over 15 portal tracts containing dense, small-to intermediate-sized lymphocytic infiltrates (Fig. 1a,b) with a small B cell population with strong PAX5 (Fig. 2a) and fewer CD20-positive cells (Fig. 2b) with co-expressed CD5 (Fig. 2c) and some CD3-positive cells (Fig. 2d). The hepatocytes showed diffuse giant cell change (Fig 1c,d). Stains were negative for CMV, adenovirus, HSV I and II. Electron microscopy showed hepatocytes with dilated mitochondria, cristae and an increase in cytoplasmic glycogen, but no viral particles were identified.

Due to the exclusion of other etiologies, the rise in her liver enzymes in the setting of a decrease in the dose of her prednisone, and the discontinuation of allopurinol for at least 6 months, the diagnosis of syncytial giant cell hepatitis was attributed to CLL. The dose of prednisone was increased to 40mg daily with a subsequent reduction in her ALT to 574U/L and AST to 158U/L in December 2014 (Fig. 3). In 20 February 2015, her ALT and AST were 388U/L and 123U/L, respectively. Given the persistent transaminitis despite high-dose corticosteroids and since the etiology of our patient's giant cell hepatitis was suspected to be a rare autoimmune complication of CLL, our patient received four cycles of rituxan on 23 February, 3 March, 10 March, and 17 March in 2015 with subsequent downtrending of her ALT and AST to 232U/L and 70 U/L in May 2015 (Table 1).

DISCUSSION

Giant cell hepatitis is a rare condition that is usually attributable to drugs, viral infection and autoimmune diseases.¹ Rather than a specific disease process, it is a nonspecific reaction to various stimuli thought to be involved in the fusion of individual cells to form a syncytium and the failure of the cytoplasm to divide upon nuclear division. After excluding viral and autoimmune causes, our patient's initial presentation was presumed to be due to the

administration of allopurinol. Allopurinol can induce a hypersensitivity reaction 2–6 weeks after its initiation, as well as different forms of liver injury including reactive hepatitis, granulomatous hepatitis or fulminant liver failure.^{12–14} Despite the resolution of her liver injury and cessation of allopurinol, our patient developed another episode of acute liver injury with repeated liver biopsy showing giant cell hepatitis and portal lymphoid infiltrate indicative of CLL. After excluding viral, autoimmune and drug-related causes, her giant cell hepatitis suspected to be linked to CLL, which is an extremely rare association.

Only three case reports associate giant cell hepatitis with CLL.^{8–10} However, these cases still link giant cell hepatitis in the context of CLL to the presence of an unknown virus. Two case reports both used electron microscopy that revealed nucleocapsid-like particles in the cytoplasm, supporting the existence of an unidentified viral species in hepatocytes as related to the disease process.^{8,9} Fimmel *et al.* argued that the patient's immunocompromised status from leukemia might have increased the patient's susceptibility for infection.⁹ Alexopoulou *et al.* referred to Phillips *et al.*, who first described syncytial giant cell hepatitis in 10 cases showing intracytoplasmic paramyxoviral nucleocapsids on electron microscopy, to suggest a paramyxovirus-like virus in his patient.^{8,15}

Our patient uniquely associated syncytial giant cell hepatitis and CLL in the absence of a viral etiology. Unlike other cases, electron microscopy in our patient showed damaged mitochondria but no intra-cytoplasmic viral particles were seen. Our case showed that CLL triggered giant cell hepatitis without the confounding presence of a virus. Another striking factor of our case was the absence of the use of chemotherapy or low immunoglobulin levels. In Gupta *et al.*'s study, the patient had hypogammaglobulinemia and received chemotherapy including chlorambucil, prednisone and rituximab.¹⁰ They concluded that these specific factors might have increased the patient's risk for giant cell hepatitis.¹⁰

Our patient had normal immunoglobulin levels and a relatively indolent course of CLL, connecting the two entities in the absence of other confounding variables. Liver injury of our patient with CLL has been the complicating factor of her disease course. The patient's WBC count was increased during both episodes of giant cell hepatitis, although confounded by prednisone use, possibly further delineating the association between giant cell hepatitis and CLL in the absence of other factors.

The treatment for giant cell hepatitis is not entirely clear, although corticosteroids and low-dose immunosuppressant such as azathioprine have been used.¹⁶ In Gupta *et al.*'s case of giant cell hepatitis in CLL, intravenous immunoglobulin and steroids were used with success, liver enzymes returned to baseline levels and remained normal for 4 years.¹⁰ Our patient successfully responded to high-dose prednisone (60mg) initially with the normalization of liver enzymes, and the medication was then tapered to 15mg. The patient's liver enzymes then skyrocketed, with a liver biopsy revealing giant cell hepatitis; therefore, the dose of prednisone was increased 40mg with an additional use of rituxan, leading to subsequent improvement in liver enzymes. This case shows that high-dose prednisone for a prolonged period of time along with rituxan may be needed in order to successfully treat giant cell hepatitis in CLL.

It is possible that CLL itself predisposes the patient to immune dysregulation, rendering lower doses of prednisone ineffective in treating syncytial giant cell hepatitis, as our patient's liver enzymes were worsened after the dose reduction to 15mg. Rituxan may also be necessary to effectively treat syncytial giant cell hepatitis caused by CLL. Rituxan, a class I chimeric anti-CD20 antibody, has found to be effective in CLL both as a single agent and in combination with chemotherapy, and it has also been used for autoimmune complications of CLL such as hemolytic anemia and immune thrombocytopenic purpura.¹⁷ Syncytial giant cell hepatitis may be yet another underlying autoimmune manifestation of CLL requiring treatment with rituxan.

In conclusion, we reported a case of syncytial giant cell hepatitis in a patient with CLL. Our patient had CLL with normal immunoglobulin levels and initially developed transaminitis after allopurinol, treatment with liver biopsy showing giant cell hepatitis, which was thought to be a drug-related condition. The patient's transaminitis was decreased with corticosteroids and the cessation of allopurinol. However, she developed another rise in liver enzymes after the reduction in prednisone with liver biopsy revealing giant cell hepatitis.

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Figure 1. Histopathological analysis of liver biopsy specimens. (a,b) Portal tracts with mixed inflammatory cells and dense small to intermediate sized lymphocytic infiltrate. (c,d) Hepatocytes with diffuse giant cell change, most predominant in periportal areas, illustrative of hepatocellular swelling and necrosis (hematoxylin and eosin stain). Magnification: a, 40×; b, 100×; c, 200×; d, 400×.

Figure 2. Immunohistochemistry showing infiltrates as a small B cell population with (a) strong PAX5 and (b) less CD20 with (c) coexpressed CD5 and (d) a minority of cells which are CD3-positive.

Figure 3.
Trend of liver enzymes. Alanine transaminase; Aspartate transaminase.

Table 1

Liver function test results and peripheral white blood cell (WBC) count

Date	ALT (U/L)	AST (U/L)	ALP (U/L)	TB (mg/dL)	WBC ($\times 10^9/L$)
2014					
21 Jun	33	34	78	0.39	65.2
7 Jul	237	159	167	0.7	60.9
14 Jul	1950	1770	227	2.5	69.1
15 Jul	2020	1670	217	2.72	88.9
16 Jul	2000	1580	199	2.26	79.1
17 Jul	1790	1230	198	2.34	83.1
22 Jul	4240	3480	266	3.9	101
23 Jul	4060	3270	233	4.76	85.8
24 Jul	4310	3210	253	5.52	95.2
26 Jul	3570	2380	242	5.54	100
30 Jul	2110	1240	229	11.43	104
11 Aug	1610	703	263	18.2	135
20 Aug	804	231	243	10.08	228
25 Aug	539	169	234	7.8	189
2 Sep	387	116	222	5.2	149
15 Sep	309	86	177	2.6	141
22 Sep	276	72	161	1.9	153
6 Oct	148	43	132	0.8	112
13 Oct	99	33	127	0.7	71.3
20 Oct	81	30	116	0.7	67.8
3 Nov	76	32	125	0.48	65.2
17 Nov	85	42	172	0.5	51.3
24 Nov	176	95	186	0.77	51.9
1 Dec	1100	626	222	1.36	51.6
4 Dec	2390	1120	228	1.54	57.1
10 Dec	1530	493	221	1.31	57.4
15 Dec	1300	360	287	1.06	70.9

Date	ALT (U/L)	AST (U/L)	ALP (U/L)	TB (mg/dL)	WBC ($\times 10^6/L$)
22 Dec	574	158	324	0.92	73.9
29 Dec	395	145	243	1.21	84.5
2015					
5 Jan	346	124	251	1.03	85.2
21 Jan	299	120	209	0.87	71
3 Feb	456	148	180	0.94	70.5
11 Feb	406	129	204	0.9	80.1
16 Feb	337	104	192	0.83	81.5
20 Feb	388	123	262	0.62	75.9
21 Feb	357	113	160	0.68	58
28 Feb	596	193	184	0.88	57.8
2 Mar	651	199	211	0.88	84.9
3 Mar	564	146	182	0.94	46.7
7 Mar	644	188	197	0.74	66
10 Mar	653	164	265	0.82	72.2
16 Mar	681	186	247	0.64	61.1
23 Mar	571	163	198	0.88	53.4
6 Apr	389	110	220	0.94	45.1
20 Apr	296	91	250	0.74	45.1
23 Apr	267	80	229	0.71	35.3
4 May	232	70	184	0.74	39.8

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; TB, total bilirubin.