Clinicopathological Conference Report

Hodgkin's Transformation of Chronic Lymphocytic Leukemia: A Rare Complication

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CASE HISTORY

A 65-year-old male presented with chief complaints of fever and difficulty in swallowing x 3 days.

Background History

In October 2014, during routine evaluation, a complete hemogram showed hemoglobin (Hb) 10.7 gm/dL, white blood cells (WBC) 22,900, 77% lymphocytes, and platelets as 1.24 lacs. On examination, he was found to have generalized lymphadenopathy and hepatosplenomegaly. Bone marrow and immunophenotyping were suggestive of chronic lymphocytic leukemia (CLL), stage Rai II Binet B. Bone marrow aspirate and hemogram findings done on October 2014 are shown in Figure 1. He was kept under observation alone; however, over the next 6 months, he developed progressive anemia and thrombocytopenia (Table 1) with on and off fever.

He was admitted (25.4.15 to 16.5.15) for further investigations. On evaluation, he showed *Staphylococcus hominis* septicemia with acute kidney injury (serum creatinine of 2.3 mg/dL), and hemophagocytic syndrome (fever, splenomegaly, cytopenias, elevated serum ferritin >1,500 ng/mL, triglycerides 250 mg/dL, and bone marrow showing hemophagocytosis with CLL). Findings of bone marrow

aspiration (BMA) done on April 30, 2015, are shown in Figure 2. He was also detected to have dilated cardiomyopathy (ejection fraction 45%). He had very high alkaline phosphatase—1,052 IU (attributed to liver infiltration). Direct antibody test was positive. After control of fever, he was initiated on prednisolone 1 mg/kg/day and cytopenias improved. On July 11, 2015, hemogram improved (Hb 10.7 gm/dL, WBC 8,770 /dL, platelets 1.07 lacs/dL). However, he had recurrence of fever and development of pancytopenia in September 2015 [Hb 5.5 mg/dL, WBC 3,000/cu mm, platelets—1 lac/cub mm, DLC P62, L24, M14]. He was started on chemoimmunotherapy with bendamustine, rituximab, and prednisolone (1 mg/kg/day). Fever subsided and hemogram improved. Wysolone was tapered and 2nd cycle bendamustine and rituximab were given. Hemogram after 10 days was normal (Hb 11.2 gm/dL; WBC 4,000 cells/cub mm, platelets 2.72 lacs cells/cub mm.)

In current admission, which was 3 days after he was seen in outpatient department, he was admitted for fever, which was moderate-to-high grade associated with dysphagia to solids. He had no cough expectoration, chest pain, or urinary complaints.

Examination

He was conscious, cooperative, had respiratory rate of 24/minute, pulse 118/minute, blood pressure 106/60 mm Hg, O₂ saturation 98% room air, and mild pallor. No icterus, clubbing, pedal edema were noted and jugular venous pressure was normal.

He had generalized lymphadenopathy (1 cm cervical, axillary, inguinal). Chest examination: Normal breath sounds, Cardiovascular system: LVS3 gallop, abdomen: spleen 4 cm, Central nervous system: normal.

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Fig. 1: Summary

Table 1: Complete hemogram

	2.4.15	18.4.15	24.4.15
Hb	9.2	8.3	6.2
WBC	19,860	11,120	5,200
Plat	86,000	46,000	30,000

Investigations (Tables 2 to 6)

S. Procalcitonin levels 0.983 (13.11.15),
17.74 (17.11.15)

Bone Marrow Aspirate and Hemogram Findings done in October 2014 (Fig. 3)

Hb: 116 gm/L; TLC: $39.1 \times 10^9/L$; Plt: $168 \times 10^9/L$; Retic: 1.3%; DLC: N 16%, Ly 74%, ProLy: 2%, Mo 6%, Eo: 2% (Abs. Lymph count: $28.9 \times 10^9/L$)

PBF:

Mild anisocytosis. Normocytic normochromic (NCNC) with a few macrocytes.

Bone marrow: Particulate, normocellular

Adequate megakaryocytes

M:E 1:1.1

Mildly megaloblastic

Bl: 1, Pm: 2, My: 10, N: 14; L: 46; Eo: 3; Ery: 24

BMA done on April 30, 2015 (Fig. 4)

Hb: 93 gm/L

TLC: $9.9 \times 10^9/L$

Plt: $22 \times 10^9/L$

Retic: 0.2%

DLC: N 61, L 33, Mo 6%; (Abs. Lymph count: $3.2 \times 10^9/L$)

Fig. 2 Richter syndrome in chronic lymphocytic leukemia

Table 2: Hemogram

Date	Hb	TLC	DLC	Platelet	MCV
12/11	10.1	1,800	P66 L22 M10 E2	74,000	
13/11	9.7	1,700	ANC 1188	72,000	83.1
16/11	7.7	1,500		34,000	80.8
18/11	8.0	7,800		37,000	75.7
19/11	8.1	7,400		23,000	74.4
20/11	7.6	4,700	P84 L6 M6 My2 MM2	17,000	77.3

Table 3: Urine examination

Date	Albumin	Sugar	M/E
13/11	+	Nil	NAD
18/11	+/-	Nil	1-2 PUS CELLS
20/11	++	Nil	Granular cast +

Table 4: Blood gas analysis

Date	pH	pO ₂	pCO ₂	cHCO ₃	SO ₂
12/11	7.524	89.4	26.6	21.4	97.9
18/11	7.498	109.2	17.5	13.3	98.6
20/11	7.393	92.9	14.5	8.6	96.8

Table 5: Biochemistry

Date	Na	K	Urea	Creat	Bilirubin (T/C)	Ca	Mg	Protein	Albumin	SGOT	SGPT	ALP	LDH	TG
12/11	127	3.7	36	0.8	0.7									
13/11	127	3.82	36	0.99	0.88	5.0	1.88	5	2.73	21	22	628	401	415
15/11	138	3.6	34	0.9	0.8									
16/11	131	3.3	45	1.43	1.32/0.69	6.8	1.66	4.7	2.41	42	27	969	275	
17/11	123	3.4	57	2.17	1.18/0.42	7.7	1.62	4.4	2.08	34	18	812		
18/11	121	3.35	83	3.12	1.45/0.63	7.4	1.53	4.8	2.18	34	13	672	660	
19/11	126	3.81	120	3.38	2.14/1.24	6.6	1.7			47	17		1,412	
20/11	122	3.64	162	4.3	3.49/2.14	6.5	1.71	4.1	1.8	42	15	699	805	

Table 6: Coaguloram

Date	PT	PTI	INR	aPTT	Fibrinogen
14/11	15	93	1.1	36	5.28

PBF:

Mild anisocytosis. Normocytic normochromic with a few macrocytes

Bone marrow particulate, cellular

Adequate megakaryocytes

M:E 1.4:1

Erythropoiesis: Normoblastic to mildly megaloblastic

Myelocytes 10, Metamyelocytes 9, Neutrophils 21, Lymphocytes 28, Eosinophils 2, Basophils 1, Erythroid precursors 29%

CXR: Normal study

ECG: Sinus tachycardia. Qs complex in V1 to V3.

Computed Tomography Chest and Abdomen: Hepatosplenomegaly with few small ill-defined hypodense lesions in liver/spleen.

Retroperitoneal and Pelvic Lymphadenopathy (Fig. 5)

USG Abdomen: Hepatosplenomegaly, no free fluid.

Barium swallow: Normal study

Stool w/u: Ova & cysts; nil

Positron Emission Tomography and Computed Tomography:

- Fluorodeoxyglucose (FDG) avid lymph nodes both side of diaphragm and FDG avid marrow lesions as described—likely Richter transformation.

- Hepatosplenomegaly with FDG avid splenic lesion and lung nodule (Fig. 6).

Course and Management

This gentleman was diagnosed as a case of CLL (intermediate risk) in October 2014 and was kept under observation. In May 2015, he had an episode of sepsis (*S. hominis* related) with acute kidney injury and hemophagocytosis and recovered with prednisolone. However, because of recurrence of symptoms in August 2015, he was given chemoimmunotherapy with bendamustine and rituximab. He had prolonged neutropenia after 1st cycle of BR and second cycle of chemotherapy was given after a delay of 19 days in the last week of October 2015. Two weeks after second cycle of chemoimmunotherapy, patient developed febrile neutropenia, dysphagia, and acute kidney injury. Dysphagia was attributed to oral candidiasis (ear, nose, and throat evaluation, Ba swallow was normal, and dysphagia recovered after fluconazole). Patient received broad spectrum antibiotics (imipenem and teicoplanin) along with hemodialysis. However, patient developed progressive hypotension and succumbed to his illness on 21st November 2015.

Case Analysis

This gentleman had a rather quick progression of CLL and a stormy course of illness. The possible reasons for such a course in this patient are: Genetic abnormalities associated with CLL. This patient had 11 q deletion (ATM

Figs 3A to D: (A) Peripheral blood film shows lymphocytosis with homogenous clump chromatin (MGG, 400X). (B) BMA shows normocellular marrow spaces with lymphocytosis (400X MGG). (C and D) Trephine biopsy Hypercellular marrow spaces with interstitial type of infiltration by atypical lymphoid cells. (200X and 400X respectively, H & E).

Figs 4A to D: Bone marrow aspiration shows normocellular marrow spaces with lymphocytosis and increase histiocytosis with hemophagocytosis (100X and 400 X respectively, MGG). (C and D) Trephine biopsy Hypercellular marrow spaces with infiltration by atypical lymphoid cells with fibrosis and Scattered RS like cells with prominent nucleoli. (200 X and 400X respectively, H & E).

(Cont'd...)

Figs 4E to H: (E-H) On immunohistochemistry, atypical larger cells shown faint expression for CD20 and intense expression for CD 30; and negative for CD 3. Increase in number of histiocytes are highlighted by CD 68 positive cells. (E-G-400X;H-100X, IHC)

gene deletion) that is generally associated with extensive nodal involvement and worse prognosis.^{1,2} Secondly, presence of advanced bone marrow fibrosis associated with significant anemia, thrombocytopenia, and 11 q deletion independently predicts prognosis.³ Thirdly, presence of hemophagocytic lymphohistiocytosis might be masquerading as progressive CLL.⁴

The reason for recurrent pancytopenia after partial recovery could be Richter transformation of CLL. Literature has highlighted that mature B cells seen in CLL can undergo transformation into Hodgkin-RS-like cells and express similar immunoprofile.⁵ In addition, Epstein-Barr virus (EBV) has been detected in HRS-like cells indicating clonal expansion of EBV harboring B cell in the setting of CLL.

The positron emission tomography computed tomography (PET CT) has a role in diagnosing Richter transformation. In one study, out of 11 patients with Richter transformation from CLL, 10 showed $SUV_{max} > 5$ ⁶ and in another study, $SUV_{max} > 13$ was associated with Richter transformation.⁷

Other complications in CLL can be infectious complications^{8,9} that are shown in Table 7.

The possible reason for cardiomyopathy in this patient could be due to endocardial fibroelastosis that might have developed due to leukemic infiltration.

Table 7 Other complications in CLL

<i>Conventional alkylator therapy</i>
Bacteria (most common)
<i>Staphylococcus aureus</i>
<i>Streptococcus pneumoniae</i>
<i>Haemophilus influenzae</i>
<i>Escherichia coli</i>
<i>Klebsiella pneumoniae</i>
<i>Pseudomonas aeruginosa</i>
Fungi (uncommon, except in heavily pretreated patients)
<i>Candida</i>
<i>Aspergillus</i>
<i>Purine analogue/alemtuzumab therapy</i>
Bacteria
<i>Listeria</i>
<i>Nocardia</i>
<i>Mycobacterium tuberculosis</i>
Atypical mycobacteria
<i>Legionella</i>
Fungi
<i>Candida</i>
<i>Aspergillus</i>
<i>Pneumocystis</i>
<i>Cryptococcus</i>
Viral
Cytomegalovirus (especially with alemtuzumab)
Varicella zoster virus
Herpes simplex virus

Figs 5A to H: Hepatosplenomegaly with few small ill-defined hypodense lesions in liver/spleen. Multiple Retroperitoneal /and pelvic Lymphadenopathy

To conclude, the febrile neutropenia might occur as a result of either accelerated transformation or Richter transformation of CLL and/or hemophagolymphohistiocytosis and/or due to chemotherapy. Sepsis would have occurred as a consequence of neutropenia that finally killed the patient.

Final Clinical Diagnosis

Chronic lymphocytic leukemia, progressive disease/ Richter transformation, on chemoimmunotherapy with BR, post 2nd cycle of BR, febrile neutropenia, acute kidney injury, dilated cardiomyopathy, refractory septic shock.

Clinical Discussion

Prof S Varma: Thank you Pankaj for the comprehensive discussion. In my opinion, I would consider HLH might be the terminal event in the patient apart from Richter transformation.

Now case is open for clinical discussion.

Prof Sanjay Jain: Cardiomyopathy and proteinuria in this patient are not explainable. I bet on amyloid in this patient. Regarding chest, I consider possibility of tuberculosis.

Dr Gaurav: There is clinicomolecular miscorrelation in this patient. 11q deletion usually presents with bulky lymphadenopathy, which is not there in this patient.

Dr Dipesh: Evidence against HLH is absence of transaminitis in this patient.

Prof Subhash Varma: I can summarize the findings in this patient. This patient had unusual course of CLL. The BM has shown HLH which partially responded to steroids. Patient also has autoimmune disorder. Patient received course of chemotherapy and he developed acute kidney injury and sepsis. Candida infection was considered during admission and patient responded to fluconazole. Otherwise, we might have thought of other infections.

ECHO during admission does not show any features suggestive of amyloid. We do not have 24-hour urine output value.

With this information, I would request Prof Amanjit to demonstrate pathology of this case.

Pathology Findings

Antemortem lymph node biopsy (S-14771/2015) showed effacement of the normal nodal architecture. The infiltrate consisted of sheets of small lymphocytes with round nuclei, condensed chromatin, inconspicuous nucleoli, and scanty cytoplasm. These cells were positive for CD20, CD23, and CD5. Background showed CD3-positive reactive T cells. Interspersed in these neoplastic cells were large pleomorphic cells, which were positive for CD30 and PAX5, but negative for LCA. No Hodgkin's milieu noted. Thus, biopsy was labeled as CLL with Reed-Sternberg like cells (Figs 7 and 8).

A *partial autopsy* was performed. On opening the serous cavities, peritoneal cavity yielded 1 L of fluid; however, pericardial and pleural cavities were within normal limits.

SPLEEN: Weighed 940 gm; was enlarged and congested. *Microscopy* showed infiltration of atypical large lymphoid cells dominantly centered on white pulp and focal spillage into red pulp. The background showed histiocytes, mature lymphocytes, and plasma cells. Focal areas of necrosis with nuclear debris were also noted. Atypical cells were positive for CD30, CD15, PAX 5, but negative for CD20, CD3, LCA. Stain for AFB negative. In addition, there was evidence of hemophagocytosis (Fig. 9).

LIVER: Weighed 2.2 kg. Grossly, liver was enlarged. The capsular surface was normal; however, the cut surface showed diffuse grayish white nodularity. Gallbladder was not identified (staples seen at site). Portal and hepatic veins were normal. Microscopy revealed preserved lobular architecture. Portal tracts were expanded and showed infiltration by atypical large lymphoid cells in a background of histiocytes, mature lymphocytes, and plasma cells along with fibrosis. Focal areas of necrosis

Fig. 6: FDG avid lymph nodes both side of diaphragm and FDG avid marrow lesions as described-likely Richter transformation. Hepato-splenomegaly with on FDG avid splenic lesion and lung nodule

Figs 7A to F: Lymph node Biopsy shows effacement of the normal nodal architecture (100X, H & E). B) Infiltrate consists of sheets of small lymphocytes with round nuclei, condensed chromatin, inconspicuous nucleoli and scanty cytoplasm. (100X, H & E). C-F) On immunohistochemistry, these cells are positive for CD20, CD23 and CD5. Background shows CD3 positive reactive T cells (200 X, IHC)

with nuclear debris were also noted. Atypical cells were positive for CD30, CD15, PAX 5, but negative for CD20, CD3, LCA. Stain for AFB-negative. Kupffer cells showed evidence of hemophagocytosis. Areas of centrilobular hepatic necrosis with reticulin collapse noted (Fig. 9).

EBV virus detection: The atypical cells were positive for EBV immunohistochemistry and Epstein-Barr encoded early RNA (EBER) ISH (Fig. 10).

Overall features are of Hodgkin's Richter transformation in chronic lymphocytic leukemia (EBV associated).

BONE MARROW: There was adequate representation of all marrow elements. A few collections of atypical lymphoid cells positive for CD30 were noted. Mild increase in histiocytes with evidence of hemophagocytosis was also present.

LUNGS: Weighed 1,200 gm, grossly both lungs were heavy, and subcrepitant. The pleura was shiny and cut surface showed peribronchiolar greyish white nodular lesions. No thrombus was seen in the major pulmonary vessels. No enlarged lymph nodes noted (Figs 11A and B). **M/E:** Sections from firm gray white lesions showed atypical lymphoid cells infiltrating the bronchial wall and peribronchiolar interstitium. These cells were positive for CD30. Focal areas of terminal bronchopneumonia and pulmonary edema were noted (Figs 11C and F).

HEART: 350 mg. Gross: The heart was flabby and showed marked dilation of all four chambers. The right ventricular wall thickness was of 0.4 cm and left ventricular

Figs 8A to D: (A) Interspersed large pleomorphic cells are seen among the neoplastic cells (100X, H &E). B-D) On IHC, these cells are positive for CD30 and PAX5 but negative for LCA(400X,IHC).

wall measures 1 cm. Valves were within normal limits, no vegetations seen (Figs 12A and B). Microscopy: showed mild endocardial fibrosis, variation in myocyte size, patchy perivascular interstitial fibrosis, and lack of inflammatory infiltrate (Figs 12C and D). Features were consistent with dilated cardiomyopathy. Aorta showed grade II atherosclerosis. Coronaries showed atherosclerotic changes with <50% occlusion of lumina.

KIDNEYS: Together weighed 320 gm. Grossly few cortical cysts and blotchiness on the surface were noted. C/S showed distinct corticomedullary junction with medullary congestion (Fig. 13A). On microscopy, glomeruli were unremarkable. Tubules showed presence of pigment casts (likely hemoglobin with fragmented RBCs) indicative of cast nephropathy. There was patchy interstitial fibrosis with fibrointimal proliferation of blood vessels (Fig. 13B).

Pancreas, Esophagus, Stomach, Small and Large Intestine, Adrenal Glands, Testes, Prostate, Bladder: Did not show significant pathological changes.

FINAL AUTOPSY DIAGNOSIS (PM-27041)

A 66-year-old male with diagnosis of CLL:

- Hodgkin's Richter transformation (EBV associated) (involving lymph nodes, liver, spleen, lungs, and bone marrow)

- Secondary hemophagocytosis
- Dilated cardiomyopathy
- Pigment cast nephropathy

Final Discussion

Prof S Varma: Yes Dr Gaurav,

Dr Gaurav: Well, I would thank Dr Amanjit Bal for performing EBV ISH in this patient. That solved most of the problems in this case. One thing EBV infection caused only HL transformation not diffuse large B-cell lymphoma (DLBCL), and other it was responsible for HLH in this patient. Other thing I want to highlight is LDH is increased one and half times in this patient that additionally supports Richter transformation in this patient.

Prof Subhash Varma: Although Dr Gaurav told most of the riddles are solved but not exactly. HLH seen in this patient may be EBV related or malignancy related. Time period is short and patient would have changes from beginning rather than developing them later. Other riddle that is not solved in this patient is the cause for pigment cast nephropathy. He also stressed that patient definitely had acute hemolytic anemia that might be responsible for pigment in this patient.

Prof Sanjay: Although signs of transformation were seen clinically and pathologically, tumor load was not

Figs 9A to J: Liver and spleen are enlarged. However, capsular surface is normal (Gross photograph). Both Liver (B) and spleen (C) show infiltration by atypical large lymphoid cells in a background of histiocytes, mature lymphocytes and plasma cells along with fibrosis. (200X, H & E). (D) Higher magnification shows atypical lymphoid cells with foci of necrosis with nuclear debris (400X, H & E). (E to J) On immunohistochemistry, atypical cells are positive for CD30, CD15, PAX 5 but negative for CD20, CD3, LCA

large in this patient. Why did the patient die?? I believe sepsis or still unenxplainable!!!

Prof Ashim Das: Patient had huge hepatosplenomegaly. Both lungs were involved extensively. Patient had extensive extranodal involvement. This is characteristic for Richter transformation to Hodgkin lymphoma. This is not true that there is no increase in tumor load.

Dr Aman Sharma: Dilated cardiomyopathy is not linked to anything, patient might have been alcoholic that could explain the cause for cardiomyopathy.

Prof Reena Das: This is extremely aggressive form of CLL. Even morphology of HL cells seen is aggressive and bizarre.

Dr Anish: If I am not wrong extensive LN involvement was shown in PET CT.

Figs 10A and B: The atypical cells are positive for EBV immunohistochemistry (A) and Epstein Barr encoded early RNA (EBER) ISH (B)

Figs 11A to F: (A and B) Both lungs are heavy, and sub-crepitant. Pleura is shiny and cut surface shows peribronchiolar greyish white nodular lesions (Gross photograph). (C and D). Microscopic examination shows atypical lymphoid cells infiltrating the bronchial wall and peri-bronchiolar interstitium (200X, H&E). (E) On higher magnification these atypical lymphoid cells are scattered among mature lymphocytes (400X, H&E). (F) These cells are positive for CD30 (400 X, H & E)

Figs 12A to D: (A and B) Heart is flabby and shows marked dilation of all four chambers (Gross photograph). (C and D) Microscopic examination shows mild endocardial fibrosis, variation in myocyte size, patchy perivascular interstitial fibrosis and lack of inflammatory infiltrate. (C-H & E; D-MT; 200X)

Figs 13A and B: (A) C/S of kidneys shows distinct corticomedullary junction with medullary congestion. (Gross photograph). (B) On microscopy, Glomeruli are unremarkable. Tubules show presence of pigment casts (likely haemoglobin with fragmented RBCs) indicative of cast nephropathy (200X, H&E)

Prof Subhash Varma concluded that we had very interesting case for CPC.

SUMMARY

B-cell CLL is an indolent neoplasm of mature B cells. About 3 to 10% of these cases undergo Richter's

transformation and give rise to large cell lymphoma, most commonly DLBCL. However, in a minority of cases, transformation into Hodgkin's lymphoma is also well known.¹⁰ In most instances, the Hodgkin's milieu on morphology and immunohistochemical features support a diagnosis of Hodgkin's lymphomatous transformation

in a case of CLL. In order to identify the origin of such HRS cells in CLL, studies have demonstrated VH gene rearrangement. In few instances, similar clonal VH gene rearrangements were identified in HRS cells and B-CLL cells, suggesting that the two cell populations were derived from a common precursor B cell. However, in other cases, in which no clonal VH gene rearrangement was demonstrable, it was concluded that a germinal center B cell, which had already acquired somatic mutations gave rise to two cell populations, one of which developed into CLL while the other into HRS cells.⁸ Evidence of EBV infection has also been documented either by EBV-LMP1 IHC or EBER ISH. Therefore, EBV infection may serve as a triggering event for the development of HRS cells in a background of CLL.

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