Concomitant Classic Hodgkin Lymphoma of Lymph Node and cMYC-Positive Burkitt Leukemia/Lymphoma of the Bone Marrow Presented Concurrently at the Time of Presentation: A Rare Combination of Discordant Lymphomas

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ABSTRACT: Discordant lymphoma is rare condition in which different types of malignant lymphomas occurring in different anatomic sites. The two diseases may present clinically as concurrent or sequential disease (10). Herein we are reporting a Pakistani female in her 60s, a carrier of hepatitis B virus with multiple comorbidities presented with cervical lymphadenopathy, diagnosed as Hodgkin's lymphoma, mixed cellularity. During the staging work-up, the patient was discovered to have extensive bone marrow (BM) involvement by Burkitt leukaemia/lymphoma (BL). Cytogenetic analysis revealed positivity for t(8;14)(q24;q32) confirmed by Fluorescence In Situ Hybridization (FISH) for IGH/MYC. Epstein-Barr virus (EBV) was demonstrated heavily in our case, with (EBV) DNA of 24,295,560 copies/ml by PCR at time of presentation, in addition, the neoplastic cells in both diagnostic tissues (cervical lymph node and BM) demonstrated positivity for EBV. A diagnosis of concomitant EBV related discordant lymphoma (classical Hodgkin lymphoma (cHL) and Burkitt lymphoma (BL) in leukemic phase was made. Among all reported cases, this case is highly exceptional because it is the first case of discordant/composite lymphoma, with this combination and concomitant presentation. Since we are dealing with a case with an exceptionally rare combination, we found it significant to elaborate more on its clinical features, contributing factors including EBV role, response to treatment, complications, and prognosis.

KEYWORDS: composite lymphoma (CL), discordant lymphoma (DL), classical Hodgkin lymphoma (c-HL), Burkitt leukaemia/lymphoma (BL), Epstein-Barr virus (EBV)

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Introduction

The simultaneous manifestation of different lymphomas in the same patient or even in the same tissue, defined as composite lymphoma (CL), is very rare. In the study of more than 1000 cases for the International Working Formulation for non-Hodgkin lymphoma (NHL), the incidence of CL varied between 1% and 4.7%.[1] Discordant lymphoma is a rare condition in which different types of malignant lymphomas occur in different anatomic sites. The two diseases may present clinically as concurrent or sequential disease.[2] Classical Hodgkin lymphoma (cHL) and NHL coexisting in the same patient are uncommon. They may occur synchronously or metachronously.[3–9]

This is a case report of a female in her 60s who presented with cervical lymphadenopathy associated with heavy infection with Epstein-Barr virus (EBV), diagnosed as Hodgkin lymphoma, mixed cellularity. During the staging workup, the patient was discovered to have extensive bone marrow (BM) involvement by Burkitt leukemia/lymphoma (BL). A diagnosis of concomitant EBV-related discordant lymphoma (cHL and BL) in leukemic phase was made.

Case Report

Here, we report a case of a Pakistani female in her 60s, a carrier of hepatitis B virus, with multiple comorbidities (diabetes type II, hypertension, dyslipidemia, and hyperthyroidism) on medications. She presented with a seven-month history of right-sided neck swelling, weight loss, and night sweating. On initial physical examination, the patient had hepatosplenomegaly and right cervical lymphadenopathy for which an excisional lymph node (LN) biopsy was performed and a diagnosis of Hodgkin lymphoma, mixed cellularity type III, was confirmed.

Histopathological examination of the LN revealed subtotal effacement of the nodal tissue by a diffuse proliferation of

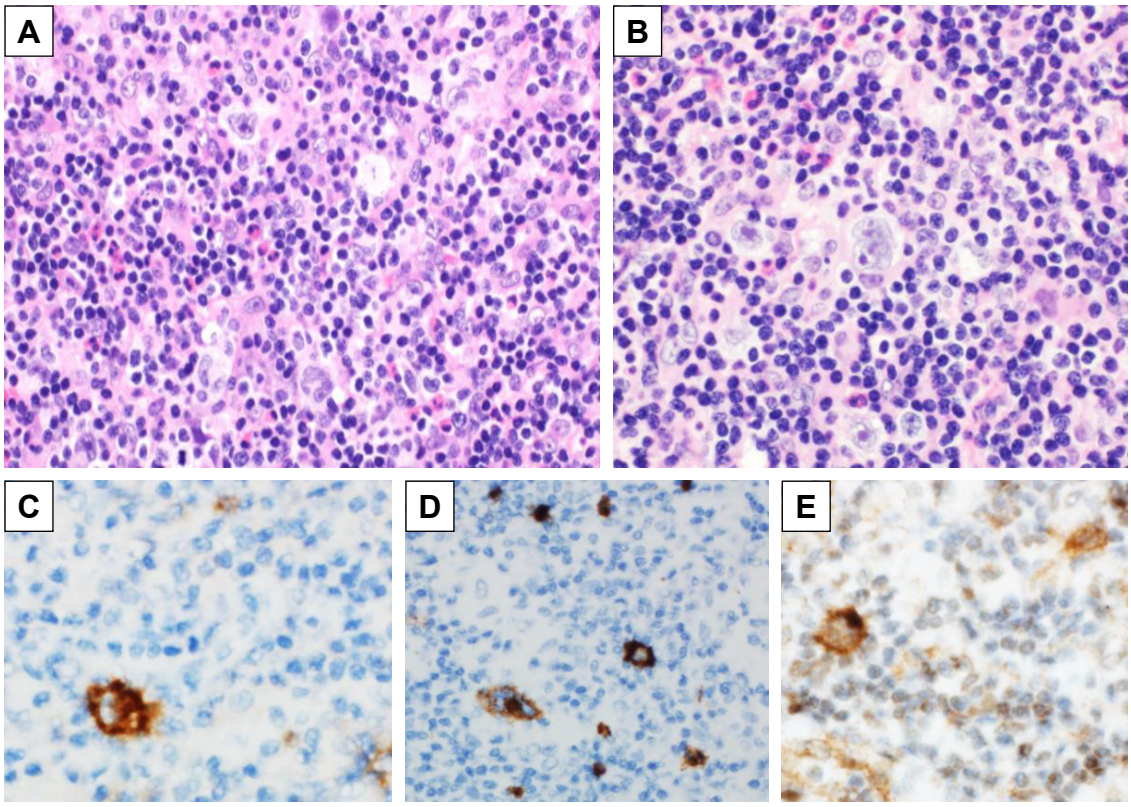

Figure 1. Histological examination. (**A** & **B**) Hodgkin/Reed-Sternberg cells seen in a reactive background of a lymph node tissue (H&E ×40). (**C** & **D**) Immunohistochemical study demonstrates that Reed-Sternberg cells are positive for CD30 and CD15. (**E**) Reed-Sternberg cells are positive for EBV (LMP-1).

lymphoid cells intermixed with scattered histiocytes, plasma cells, and eosinophils. There were many large atypical cells consistent with Hodgkin/Reed–Sternberg cells and mummified cells seen in the reactive background (Fig. 1A and B). No broad fibrotic bands were seen. Immunohistochemistry confirmed the presence of Hodgkin/Reed–Sternberg cells, as they were positive for CD30 and CD15 and negative for CD45, CD20, and CD3. EBV (LMP-1) antibody test showed that it was positive in Hodgkin/Reed–Sternberg cells (Fig. 1C–E).

The patient did not receive any sort of treatment for two months when she presented to the hematology clinic for management of Hodgkin lymphoma. At that time, she looked very sick and was complaining of generalized fatigability and severe progressive bilateral lower limb pain with inability to walk. Her physical examination in the hematology department revealed a poor general condition, with jaundice, performance status: 3, bilateral exophthalmos, diplopia, and nystagmus.

Her laboratory workup revealed markedly elevated lactate dehydrogenase (LDH) at 955 U/L [normal (n): 135–214], total bilirubin at 30 µmol/L (n: 3.5–24), low albumin at 31 g/L (n: 35–50), alanine aminotransferase (ALT) at 48 U/L, and aspartate aminotransferase (AST) at 85 U/L (n: up to 30), and markedly elevated alkaline phosphatase at 765 U/L (n: 45–129). Renal function tests were normal (creatinine: 63 µmol/L) with normal electrolytes. Hepatitis B surface antigen and hepatitis B core antibody were positive with no detectable hepatitis B virus DNA. Hepatitis C, human immunodeficiency virus (HIV), and human T-lymphotropic virus (HTLV) antibody were all negative.

EBV DNA was detected by polymerase chain reaction (PCR) at 24,295,560 copies/mL. Her CBC parameters showed mild anemia (hemoglobin: 10.8 g/dL; n: 12–15), white blood cell count: $7.8 \times 10^3/\mu L$ (n: 4–10×10^3/mL), and platelets: $195 \times 10^3/\mu L$ (n: 150–400). Peripheral smear showed mild microcytic hypochromic anemia with leukoerythroblastic picture and rare circulating leukemic cells (2%).

As the patient's general condition had rapidly deteriorated and as a part of staging workup for HL, BM examination was performed. The BM aspirate smear unexpectedly showed infiltration with monotonous population of leukemic cells (~27%), medium size with regular round nuclei, dispersed nuclear chromatin, deeply basophilic cytoplasm with prominent vacuolation (Fig. 2).

The BM biopsy was hypercellular and showed abnormal interstitial infiltrates by monotonous lymphoid population of intermediate-sized cells with multiple small nucleoli and increased mitotic figures (Fig. 3A). By immunohistochemical stains, the neoplastic cells were positive for CD20, CD79,

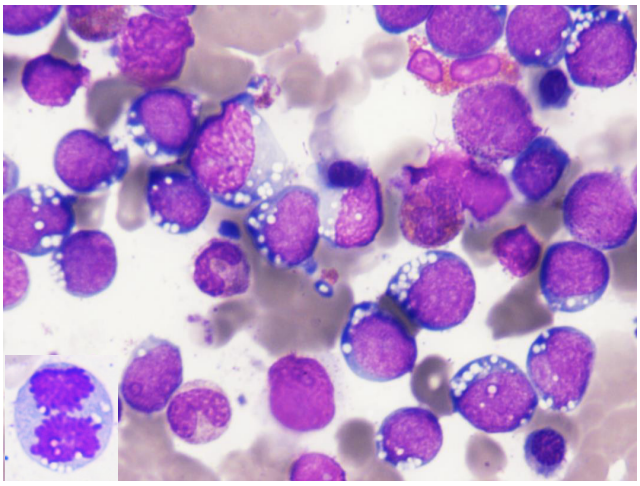

Figure 2. Bone marrow aspirate showing involvement by monotonous population of leukaemic cells deeply basophilic cytoplasm with prominent vacuolation. Insert (bottom left) shows a mitotic figure (Wright stain × 1,000).

CD10, BCL-6, c-MYC, and EBV ribonucleic acid (RNA; using in situ hybridization technique; Fig. 3B–E). Ki-67 proliferation index is more than 95% of neoplastic cells (Fig. 3F). The abnormal infiltrate was negative for CD3, CD43, TdT, and BCL-2. Reticulin stain highlighted focal increase in reticulin fibrosis in few BM areas (grade 2 out of 3). There was no evidence of BM involvement by HL.

Flow cytometry performed on BM aspirate revealed approximately 26% abnormal population of immature cells, expressing CD19, CD79b, CD20, CD10, FMC7, and CD38, with restricted cytoplasmic kappa light chain (dim expression). The B-cells were negative for CD5, CD23, CD11c, CD25, CD103, CD34, and Tdt.

Cytogenetic analysis revealed positivity for t(8;14)(q24;q32) confirmed by fluorescence in situ hybridization for IGH/MYC.

Overall findings were consistent with BM involvement by Burkitt lymphoma/leukemia.

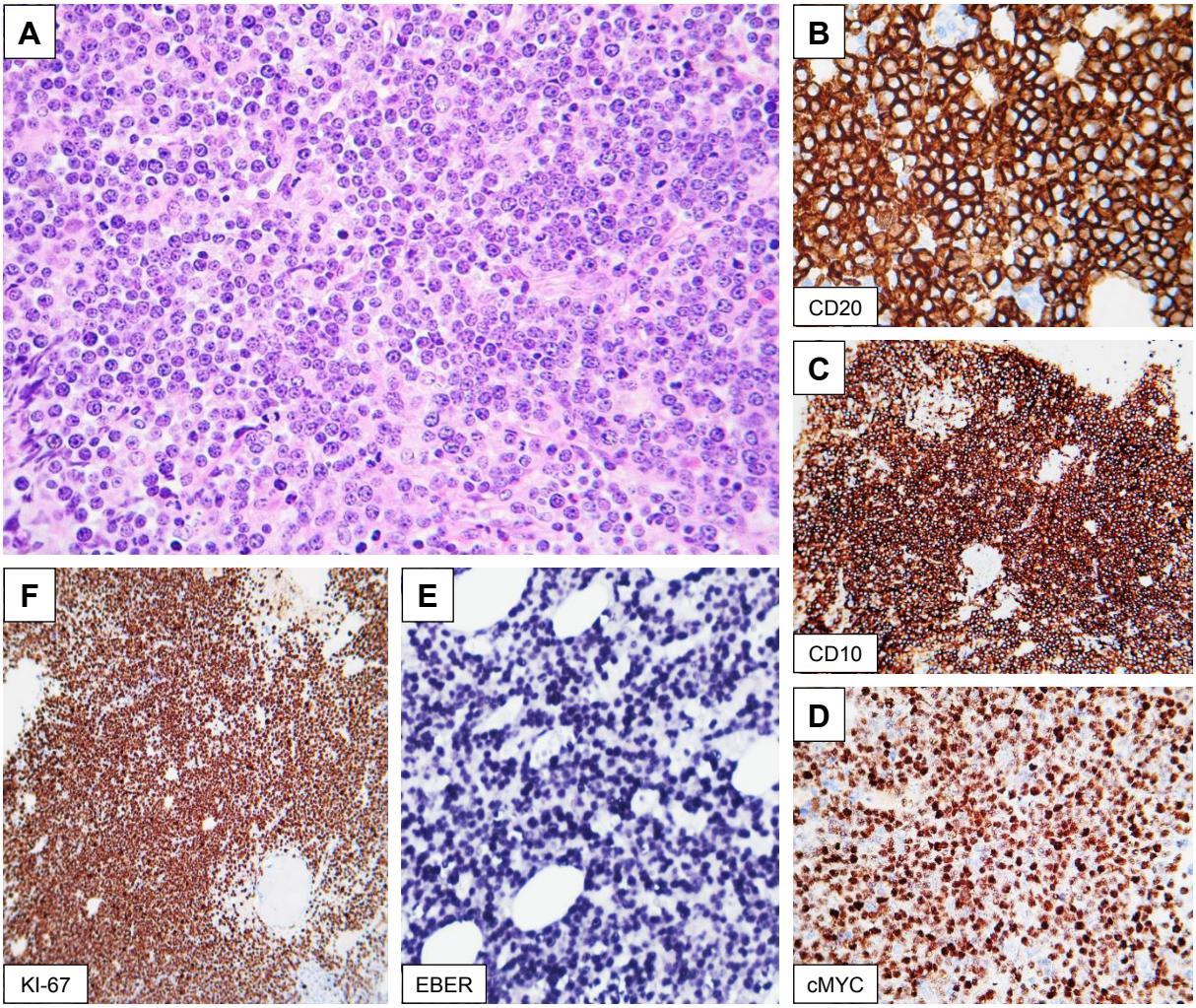

Figure 3. Bone marrow biopsy monotonous lymphoid population of intermediate sized cells with multiple small nucleoli and increased mitotic figures (**A**; H&E ×500). Immunostains on bone marrow biopsy: the lymphoma cells are positive for CD20 (**B**; 500), CD10 (**C**; 100), cMYC (**D**; ×100), EBER (**E**) and KI-67 (**F**; ×100).

Ultrasound neck showed diffusely enlarged thyroid gland with multiple nodules.

Echocardiography showed normal ejection fraction at 50%–60%. Lumbar puncture cytology was negative for lymphoma cells.

Magnetic resonance imaging of the head and spine showed lymphomatous infiltration of the skull base (clivus, basisphenoid, sphenoid sinus as well as adjacent soft tissues), with multiple variable-sized focal osseous lesions seen through the axial skeleton and extensive cervical lymphadenopathy.

Positron emission tomography/computed tomography (PET-CT) scan showed multiple affected LNs that were cervical, supraclavicular, mediastinal, and retroperitoneal stations; multiple liver, spleen, and skeletal muscle lymphomatous lesions; multiple pleural, peritoneal, extensive gastric, and sporadic bowel involvement; and multiple bone involvement; and bilateral breast and right adrenal foci also most likely representing involvement (Fig. 4A).

In order to exclude concomitant BL clone on the diagnostic LN tissue, fluorescence in situ hybridization (using IGH/MYC probes) was performed on LN that revealed a normal hybridization pattern. This is also confirmed by IHC which showed negative cMYC protein expression.

Moreover, immunoglobulin heavy chain B-cell gene rearrangement was performed by PCR on both tissues that confirmed positive B-cell gene rearrangement on BM and failed to show any evidence of B-cell gene rearrangement on LN.

Our case was labeled as EBV-derived double lymphomas; cHL type III and BL, leukemic phase with central nervous system involvement (mainly cranial nerves).

According to a multidisplinary meeting, the panel decided to give a priority for treatment of the aggressive lymphoma (BL) first. The plan was to give R-CODOX-M (rituximab, cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate)/R-IVAC (rituximab, ifosfamide, etoposide and high-dose cytarabine) regimen with management of central nervous system involvement by intrathecal chemotherapy and to be followed by radiotherapy (on the cervical and mediastinal LN) for management of HL after completion of chemotherapy.

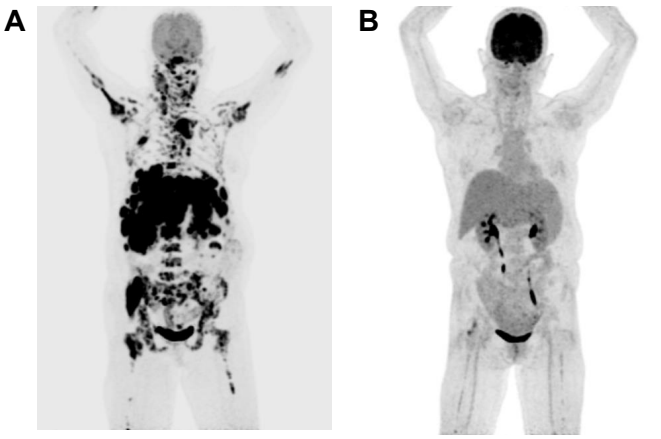

Figure 4. Positron Emission Tomography/Computed Tomography (PET-CT). (**A**) Images at diagnosis shows multiple affected lymph nodes, multiple liver, spleen and skeletal muscle lymphomatous lesions, multiple pleural, peritoneal, extensive gastric and sporadic bowel involvement, multiple bone involvement and bilateral breast involvement. (**B**) PET CT scan after two cycles of chemotherapy showed complete metabolic remission.

The patient was started initially on dexamethasone (8 mg IV every 8 hours for 5 days) and biweekly intrathecal chemotherapy [methotrexate 15 mg and hydrocortisone (50 mg)], and then she received RCVP (rituximab, cyclophosphamide, vincristine, and prednisolone) chemotherapy.

After debulking of the disease and control of tumor lysis syndrome (TLS), she was started on R-CODOX-M protocol. The course was complicated with febrile neutropenia, and the culture revealed extended spectrum Beta-lactamase producer Escherichia coli (*ESBL E. COLI*), which improved with meropenem.

The second course R-IVAC protocol was again complicated with line-related multimicrobial septicemia (*ESBL E. COLI* and *Ebterobacter Cloace*), which improved with meropenem and ciprofloxacin, along with severe electrolyte imbalance, which was corrected with electrolyte replacement.

Disease evaluation after two cycles, R-CODOX-M/R-IVAC cycle, revealed negative BM and normal cytogenetics. PET-CT showed complete metabolic remission (Fig. 4B).

The patient received the second cycle of R-CODOX-M that was also complicated with profound and prolonged febrile neutropenia exceeding two months with multimicrobial septicemia (ESBL-producing *E. coli*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*), which improved with to meropenem, colistin, and ciprofloxacin.

Because of life-threatening infectious complications, we decided to omit the last cycle of R-IVAC and to give two more cycles of rituximab followed by radiotherapy for HL.

At the end of treatment evaluation, the patient achieved very good clinical response with complete metabolic remission. The patient is alive in complete remission, but she is highly immunocompromised with multiple admissions for recurrent infection. She is on prophylactic antibiotic therapy and intravenous immunoglobulin (0.5 g/kg monthly).

Discussion

The concept of CL was first proposed by Custer[10] to denote the occurrence of more than one histological type of lymphoma in a single patient. The concept of CL is now restricted by some authors to the rare occurrence of two or more morphologically and immunophenotypically distinct lymphoma clones in a single anatomical site, ie, within a single organ or tissue.[11]

In most instances (11 of 18 informative cases), the cHL and the NHL were clonally related.[12] The reported NHL that was found to be clonally related to cHL included follicular lymphoma, mantle cell lymphoma, diffuse large cell

lymphoma, and chronic lymphocytic leukemia.[3,4,15–16] In eight of 18 combinations of a HL and a NHL that were diagnosed consecutively, the lymphomas were clonally unrelated.[12]

Most of clinically reported CLs are actually sequential lymphomas in which two different histological types of lymphoma occur in the same group of LNs after successful treatment of the first lymphoma. In these instances, the development of the second lymphoma might have been a coincidental occurrence or secondary to cytotoxic therapy received for treatment of the first lymphoma.

Discordant lymphoma is another rare condition in which different types of malignant lymphomas occur in different anatomic sites. The two diseases may present clinically as concurrent or sequential disease.[10]

According to formal description, our case is considered a discordant concurrent lymphoma as the patient has two histologically different types of lymphoma, occurring at separate anatomic sites at the time of presentation.

BL represents a unique B-cell neoplasm with a well-defined pathogenetic mechanism, as c-*MYC*/Ig translocations are considered the main genetic drive and the hallmark of BL. EBV is considered a cofactor in the pathogenesis with a very close association between EBV and BL as EBV has been detected in virtually all cases of endemic BL and some cases of sporadic BL.[14]

Regarding the association between HL and BL, the only few reported cases so far are therapy-related sequential lymphoma: a case of BL occurring in the same LN after successful treatment of nodular lymphocytes predominant HL (NLPHL) in which derivation form same clone has been proven[15] and another case of HL (nodular sclerosis) developed after treatment of BL was also reported.[16]

EBV can immortalize human B-cells and is found in the HRS cells of about 30% of cHL in developed countries. Not all subtypes of HL harbor EBV to the same degree. EBV positivity in HL tissue is highest in mixed cellularity and lymphocyte-depleted HL, while the NLPHL subtype is almost always EBV negative.[17] There are also data that suggest that the incidence of EBV-positive HL is age related, with preferential association with tumors from pediatric and older patients.[17,18]

EBV positivity was demonstrated heavily in our case, with (EBV) DNA of 24,295,560 copies/mL detected by PCR at the time of presentation; in addition, the neoplastic cells in both diagnostic tissues (LN and BM) demonstrated positivity for EBV. EBV (LMP) was detected by immunohistochemistry on LN, and Epstein-Barr encoded RNA was detected on BM biopsy by in situ hybridization. Moreover, serum EBV level had dramatically dropped down from million copies on admission to undetectable after first cycle of chemotherapy. These findings probably serve as an evidence for EBV implication in the etiopathogeneic mechanism in both lymphomas.

Inspite of the relatively long history of LN enlargement, the possibility that BL could represent a transformation of HL is very remote, since cHL does not have a tendency to transform into more aggressive subtypes unlike NLPHL, which has a tendency to transform into a high-grade lymphoma.[19] In addition, both lymphomas were detected on different anatomic sites, presented almost concurrently, with no common morphologic, immunophenotypic, cytogenetic, or molecular genetic link could be proven. As there was no evidence of concomitant BL on the LN tissue (on which HL diagnosis was originally made) and vice versa, there was no evidence of BM involvement by HL. This was also confirmed by cytogenetics (negative *cMYC*) and molecular genetics analysis that showed negativity for B-cell gene rearrangement on LN. However, this result might not be reliable as the test was not performed by microdissection technique for HRS, but the involvement by concomitant BL (on LN) has at least been excluded.

Among all reported cases, this case is highly exceptional because it is the first case of discordant/composite lymphoma, with this combination and concomitant presentation. Since we are dealing with a case with an exceptionally rare combination, we found it significant to elaborate more on its clinical features, contributing factors including EBV role, response to treatment, complications, and prognosis.

Conclusion

CL is a rare entity that is being identified and reported in recent literature.[20] Several combinations are possible with alternate pathogenesis and strict diagnostic criteria. CL must continue to be recognized because the disease subsets may have variable natural histories, prognosis, and different treatment modalities. In addition, the study of such cases may provide us with the etiology and interrelationship of clonal evolution in lymphoma.

Author Contributions

Conceived and designed the experiments: DS. Analyzed the data: DS, EA, and SF. Wrote the first draft of the manuscript: HO, MY, and AG. Contributed to the writing of the manuscript: AA. Agree with manuscript results and conclusions: AA, HO, and DS. Jointly developed the structure and arguments for the paper: DS, HO. Made critical revisions and approved final version: DS, SF, EA, HO, AG, and MY. All authors reviewed and approved of the final manuscript.

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