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Case Report

Composite Mantle Cell Lymphoma and EBV Positive Classical Hodgkin Lymphoma: A Case Report

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ABSTRACT

Composite lymphomas are two different lymphomas existing in the same location, synchronously. In the literature, composite lymphomas developed from different clones are rarely found as case reports. The coexistence of mantle cell lymphoma and classical Hodgkin lymphoma (HL) is very uncommon. The case we present was a 53-year-old male patient with a lymphocyte-rich HL in the left inguinal lymph node biopsy and a mantle cell lymphoma in the bone marrow. The diagnosis was composite lymphoma (mantle cell lymphoma + lymphocyte-rich HL) in the re-evaluation of the lymph node biopsy. Our case shows composite lymphoma developing from two separate clones (EBV positive classical HL and mantle cell lymphoma) in the lymph node and mantle cell lymphoma in the spleen and bone marrow. This case was presented and discussed because of its rarity and misleading morphology and because it is the youngest biclonal composite lymphoma with the longest survival.

INTRODUCTION

Composite lymphoma is the presence of two or more morphologically and immunophenotypically distinct lymphoma clones in a single anatomical location.[1,2] In the literature, composite lymphomas developed from different clones are rare and presented as case reports.[1,3–6] Hodgkin lymphoma (HL) is often reported to form a composite with B cell lymphomas such as follicular lymphoma, chronic lymphocytic leukemia, and diffuse large B cell lymphoma.[5,6] Here, we present a lymphocyte-rich HL, which coexists with classical mantle cell lymphoma in the same lymph node.

CASE REPORT

A 53-year-old male patient admitted to the hospital in October 2018 due to a swelling in his left inguinal region that existed for 1 year. On physical examination, there were lymphadenopathies (LAP) in the axillary and cervical regions, besides a 10 cm lymph node in the left inguinal region. The spleen was palpable subcostally. The results of laboratory examination were: white blood cells 14.90 uL (4.8–10.8), red blood cells 3.92 uL (4.7–6.1), hemoglobin 10.4 g/dL (14–18), platelets 59 uL (130–400), C-reactive protein 73.8 mg/dL (0–3.5), Beta2 microglobulin 5443 ng/dL (609–2366), and lactate dehydrogenase 369 U/L (0–248). The MRI scan of the pelvis, there were many LAP in the obturator, inguinal and parailiac areas. The largest one in the left inguinal region was 66×47 mm and in the left obturator region was 40 mm. In positron emission tomography–computed tomography (PET–CT) examination, many supra- and infra-diaphragmatic LAP were observed. In the left parailiac and inguinal areas, the largest one was 5 cm and SUVmax was 8.7; in the right axillary region, the

largest one was 2.5 cm and SUVmax was 4.4; and in the bilateral cervical chain, the largest one was 1.7 cm and SUVmax was 4. The craniocaudal diameter of the spleen was 25 cm and SUVmax was 5.3. There was activity in the bone marrow lodge with a SUVmax value of 4.5. The 5.5×4×3 cm lymph node excised from the left inguinal region macroscopically was encapsulated with a smooth surface. The cross-section was homogenous and gray colored with nodulations. In the microscopical examination, the follicular structure was effaced and sinuses were obliterated. There were nodular structures of different diameters. Nodular structures included small to medium-sized lymphocytes, rare histiocytes, a few eosinophils, and plasma cells, as well as individually scattered mono/multinuclear and binuclear atypical lymphoid cells with large vesicular nuclei and prominent nucleoli with eosinophilic cytoplasm (Fig. 1a). Immunohistochemical examination revealed a widespread positive staining with CD30, fascin, and EBV in atypical lymphoid cells, focal positive staining with CD15, and weak nuclear positive staining with PAX5. LCA staining was negative in large atypical cells (Fig. 1a–1d). CD20 was positive in most of the small lymphoid cells forming nodulation. CD3 was focal positive in nodular areas and around large lymphoid cells. The case was reported as a classical type HL lymphocyte-rich subtype due to morphology and immunohistochemistry. In the 1.3×0.2×0.2 cm bone marrow biopsy performed for staging purposes, small lymphoid cells were observed, which showed diffuse infiltration in the bone marrow and made 90% of the total population. In an immunohistochemical examination, lymphoid cells showed positive staining with CD20, CD5, and cyclin D1 (Fig. 2a), whereas CD15, CD30, CD3, CD23, CD10, Bcl-6, fascin, EBV, kappa, lambda, and LEF-1 were negative. Therefore, the diagnosis was mantle cell lymphoma classical type. After the bone marrow findings, an additional immunohistochemical examination was applied to the previous lymph node. It was found that CD20 positive small to medium-sized lymphoid cells showed positive staining with cyclin D1 and CD5 (Fig. 2b, 2c); however, there was no staining in CD30 positive large atypical lymphoid cells. As a result of the evaluation of both biopsies, lymph node biopsy was reported as composite lymphoma (HL lymphocyte-rich type and mantle cell lymphoma classical type). In fluorescence in situ hybridization (FISH)

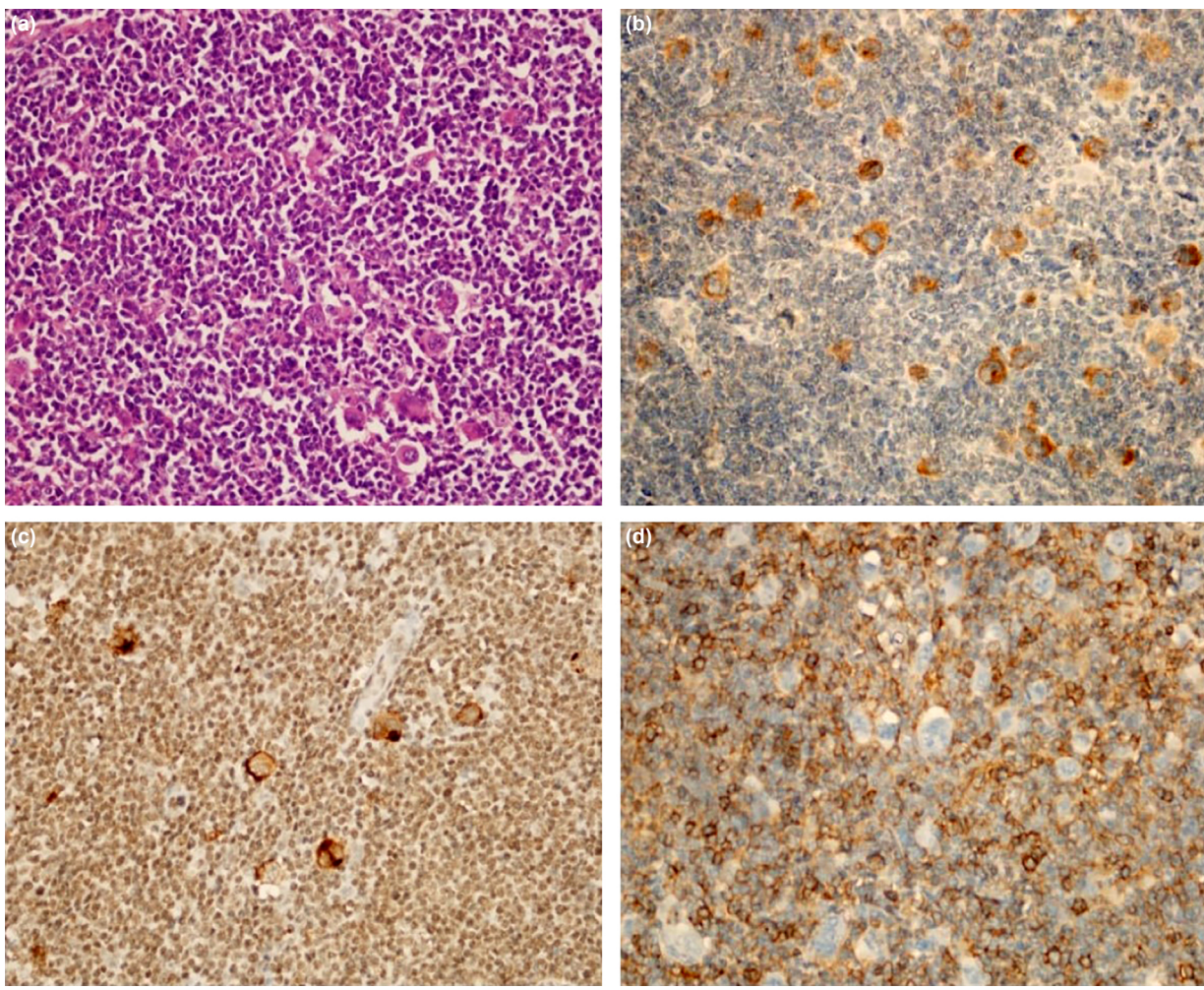

Figure 1. (a) Composite Hodgkin lymphoma and mantle cell lymphoma in the lymph node HEx20. **(b)** CD30 positive Hodgkin Reed–Sternberg cells CD30 x40. **(c)** EBV positive Hodgkin Reed–Sternberg cells EBVX40. **(d)** LCA negative Hodgkin Reed–Sternberg cells LCAX40.

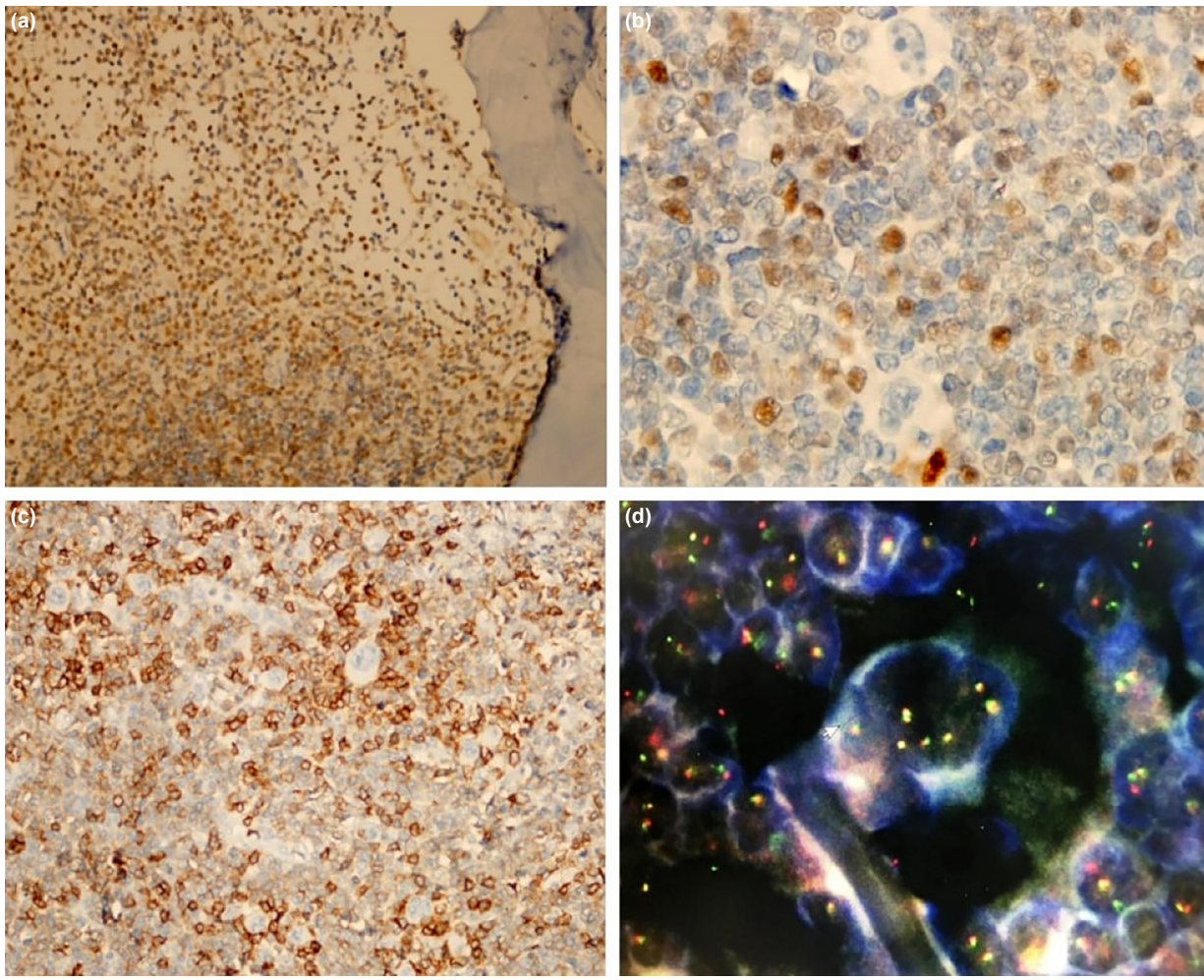

Figure 2. (a) Cyclin D1 positive lympoid cells in the bone marrow Cyclin D1x40. **(b)** Cyclin D1 negative Hodgkin Reed–Sternberg cells Cyclin d1x100. **(c)** CD5 negative Hodgkin Reed–Sternberg cells CD5x40. **(d)** In fluorescence in situ hybridization (FISH), CCND1 / IGH dual color break apart probe detected a normal signal in mantle cells and a break apart signal, while Hodgkin / RS cells did not detect a break apart signal.

examination for chromosome 11 and 14 translocation [t(11;14) (p13:q32)] for cyclin D1 rearrangement, a fusion and a break-apart signal were detected in mantle cells with CCND1/IGH dual-color break-apart probe, whereas there was no break-apart signal in Hodgkin/Reed-Sternberg cells (HRS) (Fig. 2d).

In the PET-CT examination performed after 6 cycles of R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and methyl prednisolone) treatment, there was a regression of cervical, axillary, supra- and infraclavicular, parailiac, and inguinal lymph nodes. The spleen size decreased from 25 cm to 21 cm, and the SUVmax value decreased from 5.3 to 3.7. In the bone marrow biopsy, partial regression was observed, and the findings were interpreted as a residual disease. Additionally, the patient was given 3 cycles of R-ICE (rituximab, ifosfamide, mesna, and etoposide) treatment. After this treatment, PET-CT examination showed no lymph node involvement, and the spleen size was the same. Bone marrow biopsy revealed no lymphoma involvement. The diagnosis of the patient who underwent splenectomy was reported as the classical type of mantle cell lymphoma in the spleen. Autologous stem cell transplantation was applied. After the transplantation, PET-CT examination showed complete response and no lymphoma involvement in bone marrow biopsy. The patient is in remission and has been followed for 24 months without treatment.

DISCUSSION

There is no single mechanism identified for the pathogenesis of composite lymphoma.[1] Molecular techniques showed some composite lymphomas developed from the same clone and common progenitor cells while true biclonality is present for others.[4] The fact that HRS cells in HL are derived from germinal center B cells and that most of the somatic mutations in B non-Hodgkin Lymphoma (NHL) and HL are the same support the presence of a relationship between composite follicular B NHL and HL.[2,4,7] More than 98% of RS cells in classical HL originate from germinal center B cells, whereas mantle cell lymphoma (MCL) originates from peripheral blood, primary

lymphoid follicle, and follicle mantle zone cells. Considering the origins of classical HL and MCL, it is not surprising that composite lymphoma cases are extremely rare.[4]

In the literature, 10 cases with composite MCL and HL are encountered.[1,3,8] However, it is reported that only 4 of these cases developed from two distinct clones.[1,4,5] In our case, with the use of immunohistochemistry and FISH analysis, cyclin D1 positivity and gene rearrangement were detected in mantle cells, but no mutations in HRS cells. The fact that cyclin D1 was negative in HRS cells indicated that there was no clonal relationship between the tumors. Accordingly, our case was the fifth in the literature with two distinct clones.

In the cases of true composite lymphomas reported so far, both components were seen as intertwined, but these intertwined morphological patterns were also observed in separate patterns, which facilitated the diagnosis. In the case of Caleo et al.,[6] the components in the spleen and lymph node were similar but easy to distinguish from each other morphologically. In the case of Hayes et al.,[4] HRS cells in both MCL and collagen bundles containing classical nodular sclerosing-type HL were differentiated. Giua et al.[1] detected diffuse monomorphic proliferation and the presence of HRS within that proliferation.[5] In our case, there were small lymphoid cells, forming nodular structures in the lymph node, and HRS cells distributed within the nodules. There were only a few plasma cells, eosinophils, and histiocytes that accompanied small lymphocytes. T lymphocytes formed rosettes around HRS cells. Both immunohistochemical findings and morphology suggested lymphocyte-rich HL. However, as the bone marrow biopsy performed for staging showed only mantle cell infiltration, we reviewed and reanalyzed our case and determined that small B lymphocytes in the nodulation areas were components of the mantle cell lymphoma. One of the main features that distinguish our case from previously reported cases is that the morphological pattern is misleading and both components are seen as a single mixed pattern.

The fact that both NHL and HL cells in composite lymphomas often show Epstein-Barr virus (EBV) positivity suggests an origin from a common EBV-infected progenitor cell.[4] In our case, EBV (LMP1) positivity was observed only in HRS cells, and no positivity was detected in mantle cells. That finding also supported the development of two components from different clones. Regardless of the presence of clonal association, positivity in only HRS cells implies the likely causal role of EBV in the development of CHL.[5]

Looking at the age distribution, composite lymphomas are generally seen in elderly patients and the age of patients is between 61 and 89 years.[1,3–5] Our 53-year-old patient is the youngest patient among biclonal composite MCL and HL cases.

Due to the scarcity of composite lymphomas consisting of MCL and HL, there is no clear information about their long-term follow-up, treatments, and survival. One of the patients had partial remission after 3 cycles of CHOP + fludarabine/cyclophosphamide treatment. MCL involvement in bone marrow persisted, and the patient died 11 months after the diagnosis.[4] In another case, partial remission was achieved after 6 cycles of bendamustine and rituximab treatment.[8] In the third case, a good response was achieved with 2 cycles of RCHOP and 3 cycles of adriamycin, vinblastine, and dacarbazine, but the patient was lost due to sepsis.[2] In the last case, complete remission was reported with the treatment of RCHOP, high-dose methotrexate, and folinic acid.[6] Our patient underwent autologous transplantation after RCHOP and R-ICE (rituximab + ifosfamide + carboplatin + etoposide) treatment and splenectomy. He is still in remission and followed without treatment.

CONCLUSION

Composite lymphomas are rare in the literature. The fact that the patterns are generally seen separate from each other facilitates the diagnosis. However, if it is in a single pattern, it may complicate the diagnosis and be misleading. Therefore, in lymphoma cases with morphological similarities, all neoplasms, even the least probable ones, should be considered in differential diagnosis and for accurate diagnosis, and a wide immunohistochemical panel should be applied. Our case is the youngest patient with composite lymphoma that developed from two different clones in a single morphological pattern and is the first case in the literature that has survived for 2 years after diagnosis and is still in remission.

Informed Consent

Written informed consent was obtained from the patient parents for the publication of the case report and the accompanying images.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: N.Ö.B., G.Y., C.C.B.; Design: N.Ö.B., G.Y., H.Ö.; Supervision: H.Ö., A.E.G.; Materials: C.C.B., S.H.K., A.E.G.; Data: A.E.G., G.Y., C.C.B.; Analysis: S.H.K., N.Ö.B.; Literature search: H.Ö., C.C.B.; Writing: N.Ö.B., A.E.G.; Critical revision: S.H.K.

Conflict of Interest

None declared.

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Kompozit Mantle Hücreli Lenfoma ve EBV Pozitif Klasik Hodgkin Lenfoma: Olgu Sunumu

Kompozit lenfomalar iki farklı lenfomanın aynı anda tek lokalizasyonda bulunmasıdır. Literatürde farklı klonlardan gelişmiş kompozit lenfomalar nadir olup olgu sunumu şeklindedir. Mantle hücreli lenfoma ve Klasik Hodgkin lenfoma (HL) birlikteliği çok nadir bildirilmiştir. Olgumuz 53 yaşında erkek hastadır. Sol kasığındaki lenf nodu biyopsisinde lenfositten zengin Hodgkin lenfoma, kemik iliğinde mantle hücreli lenfoma saptanmıştır. Lenf nodunun tekrar değerlendirilmesinde kompozit lenfoma (mantle hüceli lenfoma+ lenfositten zengin Hodgkin lenfoma) tanısı almıştır. Olgumuz lenf nodunda iki ayrı klondan gelişim gösteren kompozit lenfoma (EBV pozitif klasik HL ve mantle hücreli lenfoma), dalak ve kemik iliğinde ise mantle hücreli lenfoma tutulumu göstermektedir. Literatürde çok nadir olması yanıltıcı morfolojiye sahip olması, en genç ve en uzun sağ kalım gösteren biklonal kompozit lenfoma olması nedeniyle olgumuzu literatür bilgileri ışığında sunduk.

Anahtar Sözcükler: Hodgkin lenfoma; klonalite; kompozit lenfoma; mantle hücreli lenfoma.