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Case Report

Double trouble: insights from a rare case of extranodal composite lymphoma in an elderly man, with comprehensive literature review

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Abstract: Composite lymphoma (CL) is a rare cancer characterized by the concurrent occurrence of more than one type of lymphoma within the same organ or tissue in an individual. Its occurrence at extranodal sites is exceptional, with only a few cases documented in the literature. A 62-year-old gentleman presented with dystonia, dysphagia, and irregular enlargement of the right tonsil for the last three months. Based on a clinical suspicion of tonsillar malignancy, tonsillectomy was done. The histopathologic examination revealed effacement of the architecture by large irregular lymphoid nodules with interfollicular expansion. The nodules showed sheets of small atypical lymphoid cells, while the interfollicular areas showed large atypical lymphoid cells with scattered typical binucleate Reed-Sternberg cells. Immunohistochemistry confirmed mantle cell lymphoma (MCL) in the nodules and classical HL (cHL) in the interfollicular areas. Based on these features, a diagnosis of composite MCL with cHL was rendered. He was treated with bendamustine and rituximab chemotherapy and remained in complete remission for five years when he presented with significant right-sided neck swelling. Percutaneous fine needle aspiration and subsequent flow cytometry confirmed a relapse of the MCL component of the CL. The index report documents an exceptional case of CL, comprising MCL and cHL, presenting at an uncommon extranodal site. In addition, it also emphasizes the importance of adequate sampling and the simultaneous use of immunochemistry and/or flow cytometry to confirm the presence of more than a single type of lymphoma, which may be easily overlooked on microscopy alone.

Keywords: Composite lymphoma, mantle cell lymphoma, Hodgkin lymphoma, immunohistochemistry, relapse, flow cytometry, fine needle aspiration cytology

Introduction

Composite lymphoma (CL) is a rare disease characterized by simultaneous occurrence of more than one type of lymphoma within the same organ or tissue in an individual [1]. The disease has an estimated incidence of around 1.0-4.7% of all newly diagnosed lymphomas annually [2]. It is more common above 50 years of age with a slight male preponderance [1, 3]. Pathologically and immunophenotypically, CL is characterized by the simultaneous presence of non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL), or histiocytic or dendritic cell tumor. Furthermore, it can demonstrate a combination of B-cell NHL with T-cell NHL or the coexistence of T-cell or B-cell NHL with other subtypes of the same lineage [1, 4]. The most common CL is the co-occurrence of classical Hodgkin lymphoma (cHL) with a low-grade follicular lymphoma (FL), followed by the combination of cHL with a diffuse large B-cell lymphoma (DLBCL) and in third place, mantle cell lymphoma (MCL) co-occurring with FL [4-7].

The diagnosis of CL mandates the morphologic and immunophenotypic demonstration of two distinct types of lymphoma in the same tissue. Fine needle aspiration cytology (FNAC) is a commonly used procedure to evaluate lymph nodal masses with considerable sensitivity and specificity [8]. With the frequent use of flow cytomet-

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ric immunophenotyping (FCI) on fine needle aspirates, it has become possible to render precise diagnoses for various hematolymphoid malignancies, including both B-cell and T-cell lymphomas [9, 10]. Nonetheless, diagnosing CL on FNAC is challenging, since the needle might not sample the area harboring the second type of lymphoma. However, obtaining multiple passes from different areas can help minimize such sampling errors. Furthermore, a part of the aspirate should also be collected for flow cytometry, cell block preparation, and immunocytochemistry (ICC). Both ancillary procedures, FCI and ICC on cell block sections, may help characterize the distinct lymphoma types and establish the diagnosis. Histopathologic examination with immunohistochemistry and/or flow cytometry remains the gold standard for diagnosing CL. Histopathologically, CL typically exhibits a combined pattern or, less frequently, a discernible zonal distribution of the individual lymphoma components [4, 10].

A majority of CLs follow an aggressive course. Owing to the rarity of the disease, standard treatment guidelines are unavailable. The treatment varies depending on the histologic subtype. Most commonly, first-line chemotherapy with alkylating agents is used, and rituximab is added for CD20-expressing B-cell lymphoma. However, relapses are frequent despite treatment and usually present as the higher-grade subtype [1, 10]. Herein, we describe the characteristic pathologic and immunophenotypic features of a composite lymphoma (MCL and cHL) in a man, which relapsed as MCL after remission.

Case report

A 62-year-old gentleman presented with a history of voice change and difficulty swallowing for three months. On examination, there was an irregular mass arising from the right tonsil. A clinical suspicion of tonsillar carcinoma was considered, and the patient underwent tonsillectomy.

The histopathologic examination of the tonsil revealed an architecture completely effaced by irregular follicles forming large lymphoid nodules with interfollicular expansion. The nodules comprised a monomorphic population of small atypical lymphoid cells with cleaved nuclei, condensed chromatin, and scant cytoplasm. The interfollicular areas showed large atypical lymphoid cells with abundant cytoplasm, round-oval nuclei, vesicular chromatin, and prominent eosinophilic nucleoli. Occasional binucleate Reed-Sternberg cells were seen along with cells with polylobated nuclei. The background showed a polymorphous population comprising small lymphocytes, few plasma cells, histiocytes, and many eosinophils. These large atypical cells were also identified within the follicles, thus suggesting a mixed pattern of CL.

By immunostaining, the lymphoid cells in the nodules were positive for CD20, Cyclin D1, SOX11, and BCL2 and negative for CD5, CD23, and BCL6, confirming a diagnosis of mantle cell lymphoma. Additionally, the large atypical lymphoid cells showed membranous positivity for CD30 and faint nuclear positivity for PAX5 and were negative for CD45, CD20, and CD3, confirming the immunophenotype of Reed Sternberg cells. CD3 and CD20 highlighted the background reactive lymphocytes in the interfollicular areas (**Figure 1**). Based on morphology and immunohistochemistry, a diagnosis of composite MCL with interfollicular cHL was rendered.

A staging bone marrow examination showed infiltration of the marrow by mantle cell lymphoma. This was confirmed by flow cytometry performed on the bone marrow aspirate. The patient was treated with six cycles of bendamustine and rituximab combination chemotherapy, with which a complete remission was achieved. Rituximab maintenance therapy was given for the next two years. He remained in complete remission for the next five years until he presented with significant right-sided neck swelling associated with fever, loss of appetite, and weight loss. Positron emission computerized tomography revealed a metabolically active, large soft tissue mass with intracranial and extracranial components involving the nasopharynx, oropharynx, right orbit, and right infratemporal fossa. Findings were suspicious for relapse.

Percutaneous fine needle aspiration was performed from the neck mass. Air-dried and alcohol-fixed smears were prepared, and part of the aspirate was collected for flow cytometric immunophenotyping. The cytologic smears were cellular, showing a dispersed monomorphic population of small to intermediate-sized atypical lymphoid cells with angulated nuclei,

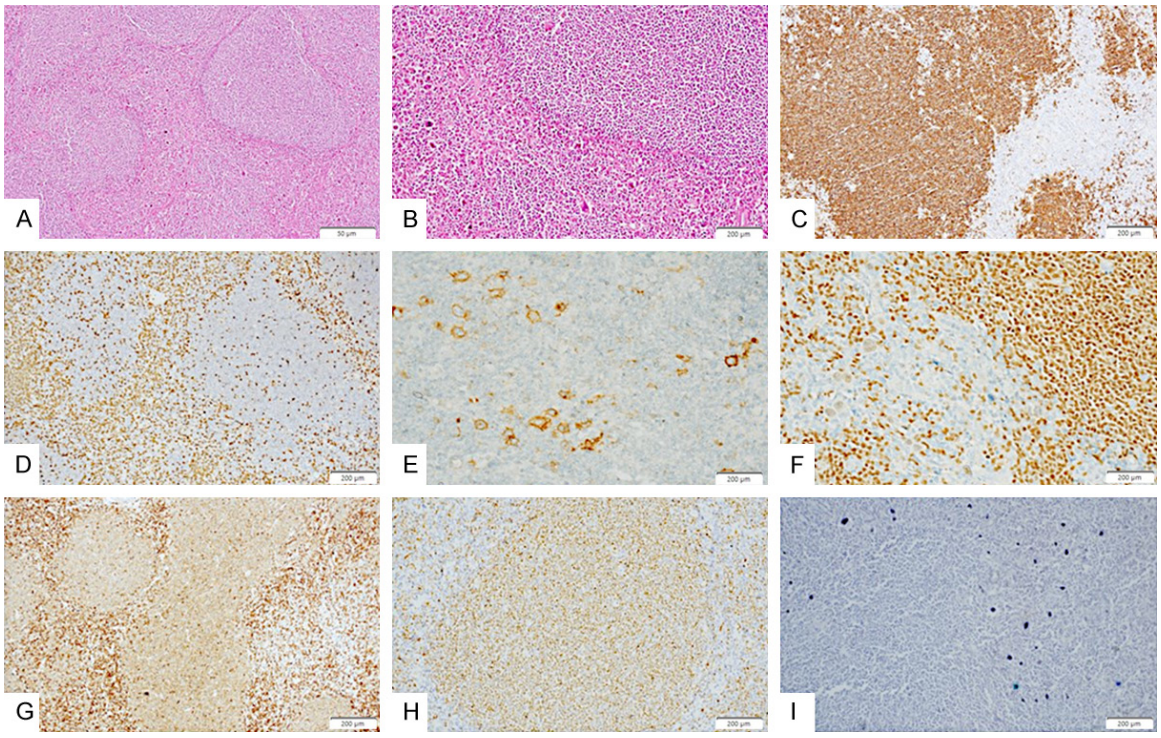

Figure 1. (A, B) Section from the tonsil showing large lymphoid nodules with interfollicular expansion. The nodules showed a monomorphic population of small atypical lymphoid cells. The interfollicular areas showed large atypical lymphoid cells with prominent eosinophilic nucleoli. Occasional binucleate Reed-Sternberg cells were also seen in a background of a polymorphous population comprising small lymphocytes, few plasma cells, histiocytes, and many eosinophils. Few large atypical cells were also noted within the follicles (H&E; A: 10×, B: 20×); (C-I) Immunohistochemistry showing lymphoid cells in the nodules to be positive for CD20 (C; 20×), Cyclin D1 (H; 20×), SOX11, and BCL2, weak CD5 (G; 20×), and negative for CD23, and BCL6, confirming the diagnosis of mantle cell lymphoma. The interfollicular large atypical lymphoid cells showed membranous positivity for CD30 (E; 20×) and Epstein-Barr encoding region in situ hybridization (EBER-ISH; I; 20×), faint positivity for PAX5 (F; 20×), and were negative for CD45, CD20, and CD3 (D; 20×), confirming the immunophenotype of Reed-Sternberg cells.

clumped chromatin, and scant cytoplasm. Around 10-15% of these cells showed open chromatin, indicating blastoid morphology. No Reed Sternberg-like cells were identified (**Figure 2**).

Immunophenotyping by flow cytometry was performed. Of all the viable cells, CD45-positive low-side scatter cells were gated. Around 93% of these cells were CD19-positive B-cells, which were also positive for CD5, CD43, and HLA-DR, and showed lambda light chain restriction. These cells were negative for CD10, CD34, CD23, and CD200. CD3-positive T-cells amounted to 5% and showed no aberrant expression of CD markers. Overall features were consistent with relapse of the MCL component of the composite lymphoma (**Figure 3**). The patient was started on chemotherapy for relapse but succumbed to cancer after six months.

Discussion

Composite lymphoma is a highly infrequent cancer characterized by the simultaneous occurrence of two or more distinct lymphomas in the same body part [1]. The annual incidence rates vary from 1-4%; however, the exact incidence may be underestimated since one of the tumor components may be subtle and be overlooked during the initial microscopic examination [4, 5]. This emphasizes the importance of immunophenotyping by immunohistochemistry or flow cytometry to confirm the diagnosis. CL usually occurs in older adults with a slight male preponderance, as in the current case.

The exact etiopathogenesis of composite lymphoma is not known. However, molecular studies in most CLs indicate a clonal association between both types of lymphoma. Contrary to the earlier belief, composite lymphomas do not

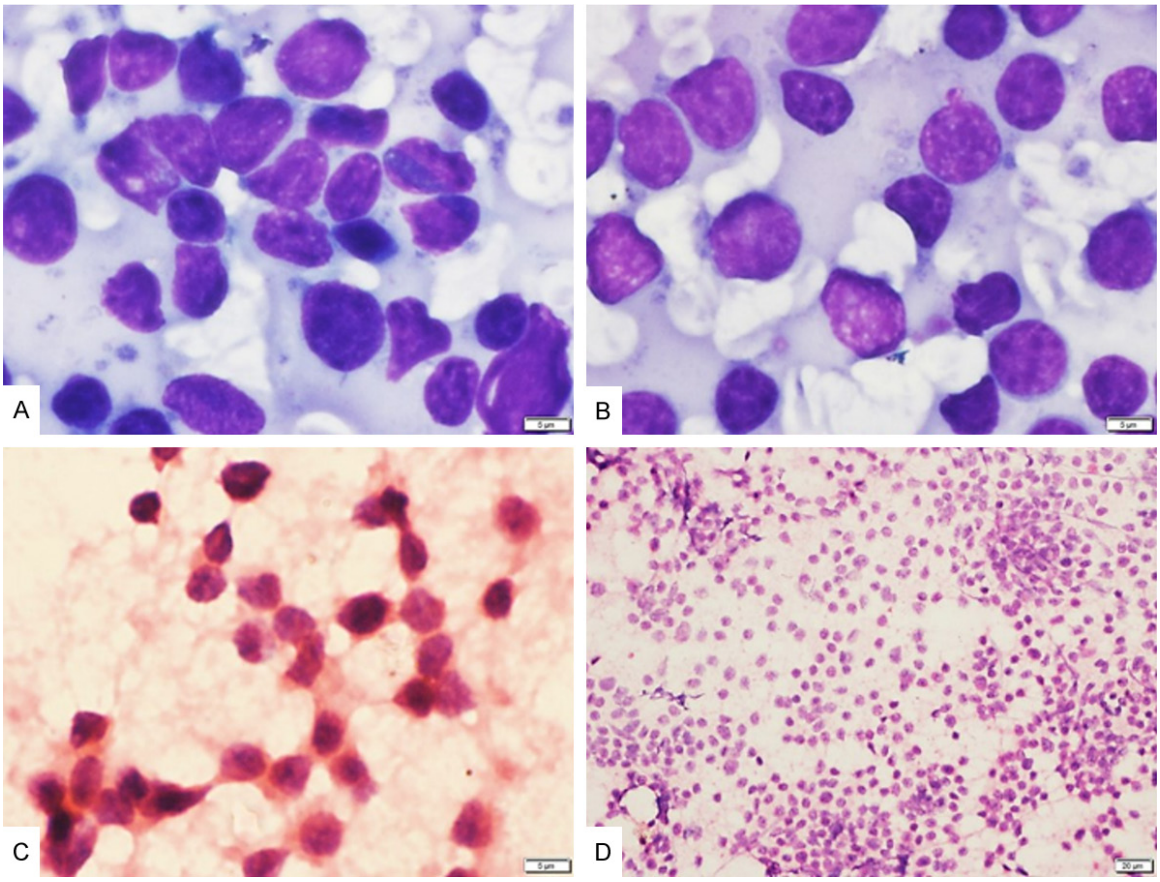

Figure 2. (A-C) Cellular smears showing a dispersed population of atypical lymphoid cells, which are 2-2.5 times the size of a small mature lymphocyte, angulated nuclei, open chromatin, inconspicuous nucleoli, and scant cytoplasm. The background shows few mature lymphocytes and many lymphoglandular bodies (A, B: MGG; 100×) (C: H&E; 100×); (D) Section from the cell block showing dispersed atypical lymphoid cells with similar morphology (H&E; 20×).

develop due to the transformation of one lymphoma into another. Instead, they develop from the simultaneous evolution of two distinct malignant cell populations from a shared, premalignant precursor cell in the multistep transformation process of lymphomagenesis. Additionally, researchers have documented several shared genetic abnormalities in these cases. These include frequent gene translocations involving BCL2, BCL6, and CCND1, as well as common rearrangements of the IgH and/or IgK genes, encoding the heavy and light immunoglobulin chains [11-13].

Nodal presentation is more common than extranodal involvement in patients with CL, with extranodal involvement limited to occasional case reports [14, 15]. The patients usually present with B-symptoms and lymphadenopathy. To date, only a single case of CL involving the tonsils has been described in the literature [15]. While radiologic investigations and bone marrow examination are pivotal for staging the disease, cytologic/histopathologic examination along with immunochemistry and/or flow cytometry remains the gold standard for confirming the diagnosis.

Cytologic smears may show a dispersed population of atypical lymphoid cells. Two distinct populations of atypical cells may be evident on the smears; however, if one of the lymphoma components is subtle and multiple areas have not been targeted on fine needle aspiration, it may be easily missed. Flow cytometry and immunocytochemistry on cell block help in substantiating the diagnosis. Histopathology mostly shows the two distinct lymphoma components intermixed with each other. The most common lymphoma components in CL include

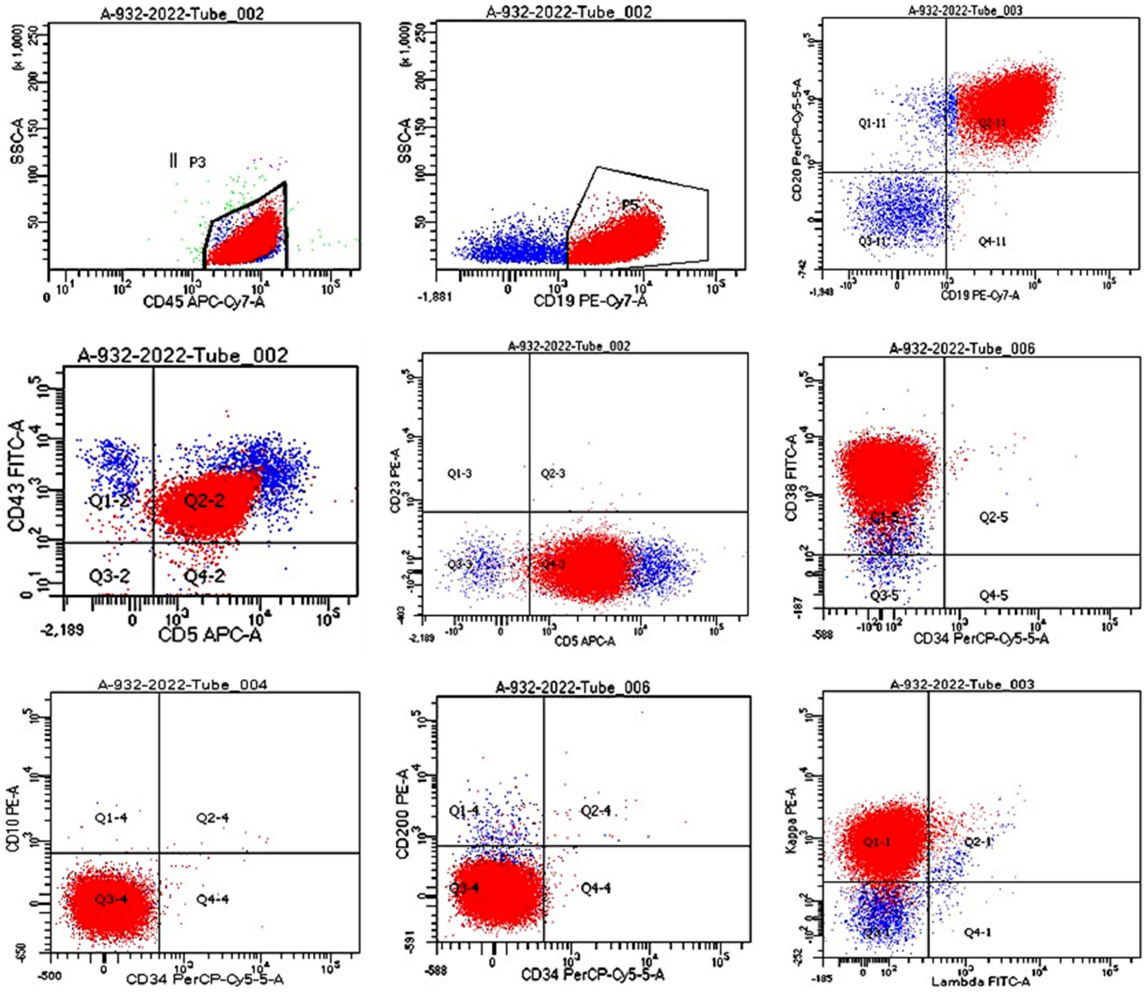

Figure 3. Flow cytometric immunophenotyping on the fine needle aspirate. The atypical lymphoid cells were positive for CD19, CD5, CD43, CD38, and showed kappa light chain restriction. These cells were negative for CD23, CD3, CD34, CD10, and CD200.

cHL associated with a low-grade FL [4-7]. A composite lymphoma showing cHL associated with MCL (as in the current case) is extremely rare, with only 12 cases reported in the literature so far (**Table 1**) [1, 12, 15-23]. Of these documented cases, only four presented with extranodal involvement, as in the current case.

The clinical course and treatment of CL vary depending on the histologic subtypes. Composite lymphomas, depending upon subtypes, generally display a more aggressive clinical course compared to specific lymphoma types. Relapses are frequent, and relapse can present as CL or one of its components [1, 10]. In the current case, the patient was diagnosed with CL comprising MCL and cHL of the tonsil and received chemotherapy; however, he relapsed five years later, as MCL involving the infra-auricular soft tissues.

Conclusion

This index report documents the characteristic pathologic and immunochemical features of a rare case of composite lymphoma, comprising mantle cell lymphoma and classical Hodgkin lymphoma, presenting at an uncommon extranodal site. In addition, it also emphasizes the importance of adequate sampling and the use of immunochemistry and/or flow cytometry to confirm the presence of more than a single type of lymphoma, which could be easily overlooked by morphology alone.

Table 1. Review of the literature highlighting documented cases of composite lymphoma comprising classic Hodgkin lymphoma and mantle cell lymphoma [1, 12, 15-23]

S. no.	Author	Year	Site at presentation	Composition of the primary tumor	Relapse	Site of relapse	Composition at relapse
1.	Current case	2023	Right tonsil	MCL + cHL	Yes	Infra-auricular soft tissue swelling	MCL
2.	Wang H, et al. [23]	2023	Axillary lymph node	MCL + cHL	-	-	-
3.	Gui W, et al. [1]	2020	Inguinal lymph node	MCL	Yes	Submaxillary lymph node	cHL + MCL
4.	Tashkandi H, et al. [21]	2019	NA	MCL	Yes	First relapse: Inguinal and hilar lymphadenopathy Second relapse: Acetabulum	First relapse: cHL Second relapse: Blastoid MCL
5.	Kramer S, et al. [22]	2019	Orbit	MCL	Yes	Disseminated disease	MCL + cHL
6.	Sharma S, et al. [15]	2019	Right tonsil	MCL + cHL	-	-	-
7.	Murray C, et al. [20]	2017	Generalized lymphadenopathy	MCL + cHL	-	-	-
8.	Giua R, et al. [19]	2015	Axillary lymph node	MCL + cHL	-	-	-
9.	Schneider S, et al. [12]	2014	Peripheral blood	MCL	Yes	Cervical lymphadenopathy	cHL + MCL
10.	Hayes SJ, et al. [18]	2006	Axillary lymph node	MCL + cHL	-	-	-
11.	Tinguely M, et al. [17]	2003	Abdominal lymph nodes	MCL	Yes	Abdominal lymphadenopathy	cHL + MCL
12.	Caleo A, et al. [16]	2003	Eyelid mass	MCL + cHL	-	-	-
13.	Caleo A, et al. [16]	2003	Spleen	MCL + cHL	-	-	-

MCL, mantle cell lymphoma; cHL, classical Hodgkin lymphoma.

Disclosure of conflict of interest

None.

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