Composite Lymphoma

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Abstract. Composite lymphoma is the presence of different morphological types of lymphoma in a single lymph node at the time of clinical presentation. It is a rare type of lymphoid neoplasm, present in lymphoid tissue. This paper is presenting four rare cases of composite lymphoma identified in our clinical practice. Three of the cases were female: one with inguinal mass, second with cervical lymph nodes enlargement, and the third with enlarged tonsils. The fourth case was a male presented with enlarged tonsils. The patients' ages ranged between 40-54 years. Histopathological examinations and immunohistochemistry features proved the diagnosis of composite lymphoma. Two of the cases presented with a rare association of Hodgkin's and non-Hodgkin's lymphoma The third case represents two different types of non-Hodgkin's lymphoma, and the fourth case represents a rare association of high grade non-Hodgkin's lymphoma and low grade follicular center cell lymphoma. The authors discuss, in detail, these four cases and review the literature of similar association.

Keywords: Composite lymphoma, Hodgkin's and non-Hodgkin's lymphoma.

Introduction

Composite tumor by definition is the presence of two distinct malignancies in the same topographic site at the time of presentation.

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Composite lymphoma (CL) was first defined by Custer^[1], and later a modified definition was done by Hicks et al. [2] and Kim et al. [3] as the presence of two distinct architectural and cytological subtypes of lymphoma occurring in the same anatomic site or tissue, i.e., biphasic expression of the same neoplastic clone. It is different from the term discordant lymphoma, which describes two different types of lymphoma that occurred at separate anatomic sites at the time of presentation and sequential lymphoma in which two different histological types of lymphoma occur in the same group of lymph nodes following one another. The majority of diagnosed CL represents two forms of non-Hodgkin's lymphoma (NHL), e.g., mixed small and large cell lymphoma. The rare association is the presence of Hodgkin's lymphoma and NHL in the same lymph node, and it is believed that Hodgkin's and NHL represent mutually exclusive clinicopathological entities^[4]. In this paper, four rare cases of CL are presented. Two of them were Hodgkin's and non-Hodgkin's. The third and fourth cases of CL were of a different histological subtype of NHL.

Material and Results

Case 1

A forty-year-old Sudanese pregnant female (gestation: 25 wks) was referred to the surgical clinic because of a large left groin mass. The mass was excised. It was composed of two well-circumscribed masses. The largest one measured 5.5×5 cm diameter and the smaller measured 3×3 cm diameter. These masses revealed a white firm cross section with slimy appearance and focal nodules at one edge of the specimen with no variegation of colors or necrosis. Histological examinations revealed two distinct morphological patterns at the nodular edge. There was nodular proliferation of small and large lymphocytes exhibiting oval nuclei with convolution of nuclear membrane and indistinct cytoplasm. Mitosis was seen. The tumor cells were present in nodules that were well accentuated by reticulin stain (Fig. 1a). An adjacent area to this architecture was diffuse mixed inflammatory cells infiltrate composed of eosinophils, plasma cells, and histiocytes, as well as large mononuclear cells and multinucleated cells (Fig. 1b). The latter exhibited some large nuclei with prominent nucleoli and abundant amphophilic cytoplasm representing typical Reed-Sternberg cells (RSC) and its mononuclear variant, as well as lacunar and convoluted lymphocytic/histocytic (L/H) variant were present (Fig. 1c).

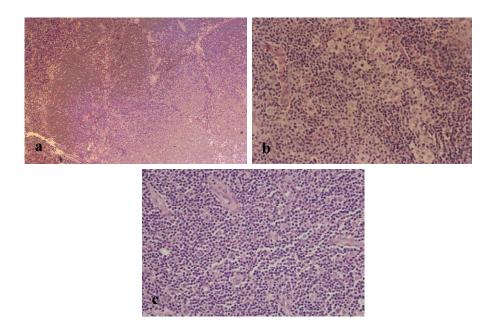


Fig. 1. (a) Low power 4× – mixed follicular small and large B cell lymphoma,

- (b) High power of mixed follicular small and large B cell lymphoma.
- (c) RSC in typical Hodgkin's lymphoma background.

Panels of antibodies were performed which included LCA, CD20, CD45 RA, CD45 RO, CD5, BCL2, and BCL6. The results for these stains are presented in Table 1. The final diagnosis of this case was CL non-Hodgkin's nodular mixed small and large B-cell phenotype and Hodgkin's lymphoma mixed cellularity type. Bone marrow biopsy was negative for lymphoma infiltrate. The patient received chemotherapy (CHOP) 3 cycles before delivery and she had a caesarian section at 36-weeks of gestation. She gave birth to a baby boy 3.5 kg birth weight. The baby was well up to the time of this report. The patient was ready to continue her CHOP.

Table 1. Case 1 Immunohistochemistry (DAKO Antibodies).

Immunohistochemistry Panel			
Antibodies	Specificity	Results	
		NHL	HL RSC
LCA +	Lymphocytes/ leukocyte common antigen	+	-
CD20 +	B cell	+	-
CD45 RA +	B cell	+	-
CD45 RO –	T cell	+	-
CD5 –	T cell	_	-
Bcl 2 + (80%)	Fcc	+ 80%	-
Bcl 6 –	Lymphocytes	_	-
CD30	RSC	_	+
CD15	RSC	_	+

NHL = Non-Hodgkin's Lymphoma

HL RSC = Hodgkin's Lymphoma Reed-Sternberg Cells

RSC = Reed-Sternberg Cells FCC = Follicular Center Cells

Case 2

This case represents a 52-year-old female presented with right cervical mass that increased in size for 6 months duration. No other associated symptoms. The mass was excised and material was submitted to the Histopathology Department. The mass measured $3.5 \times 2.5 \times 2$ cm diameter. The cut section revealed white firm areas with slimy appearance and scattered small nodules. Microscopically the tumor was composed of well-defined small nodule exhibiting predominantly small lymphocyte with cleaved nuclei, indistinct nucleoli small cytoplasm, and occasional mitosis. There were also bigger nodules composed mainly of mature lymphocytes, epithelioid cells, neutrophils, and few eosinophils. Mononuclear large cells and binucleated RSC as well as lacunar variant of RSC and hyperlobulated ones were also seen. No necrosis was seen. (Fig. 2a-c). See Table 2 for immunohistochemistry of this case. The patient's diagnosis was CL, non-Hodgkin's follicular center cell lymphoma (FCCL) predominantly small lymphocyte, B-cell phenotype and classic Hodgkin's lymphoma, nodular sclerosis, variant.

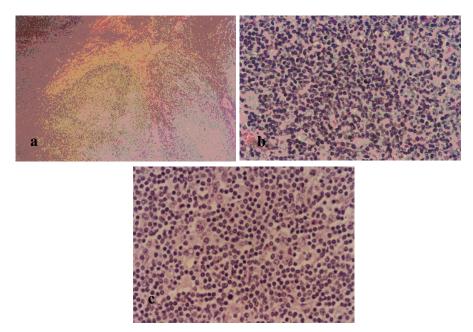


Fig. 2. (a) Low power 4× of nodular sclerosis Hodgkin's lymphoma,

- (b) High power 40× of non-Hodgkin's follicular small lymphocytes B cell phenotype,
- (c) High power 40× of typical RSC of Hodgkin's lymphoma.

Table 2. Case 2 Immunohistochemistry (DAKO Antibodies).

Immunohistochemistry Panel			
Antibodies	Specificity	Results	
		NHL	HL RSC
LCA	Leukocytes common antigen	+	_
CD20	B cell	+	-
CD22	B cell	+	-
Bel2	Fee	+75%	-
CD5	T cell	_	-
CD15	RSC	1	+
CD30	RSC		+
EMA	Epithelial membrane antigen	_	_

NHL = Non Hodgkin's Lymphoma

HL RSC = Hodgkin's Lymphoma Reed-Sternberg Cells

RSC = Reed-Sternberg Cells FCC = Follicular Center Cells

Case 3

A fifty-two-year-old male had been referred to King Abdulaziz University Hospital (KAUH) with an enlarged right tonsil. The tonsil was resected and grossly measured $3.8 \times 3 \times 2$ cm. Cut sections revealed white firm homogenous nodules. Microscopic sections revealed effaced nodal architecture with the formation of variable sized nodules composed mainly of small-cleaved lymphocytes, and large lymphocytes with vesicular chromatin and prominent central nucleoli. Areas of diffuse cellular growth, composed predominantly of large lymphocytes, were also seen (Fig. 3a-c). See Table 3 for immunohistochemical study of this case.

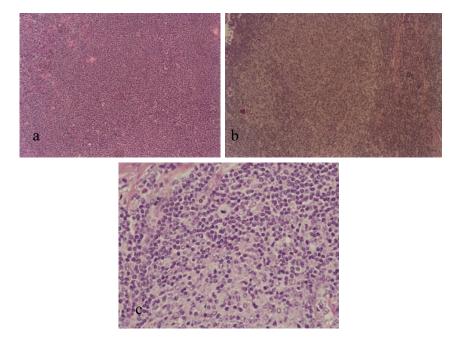


Fig. 3. (a) Low power $4\times$ and High power $40\times$ of diffuse large cell lymphoma B cell phenotype,

- (b) Low power 10× nodules of small and large B cell phenotype, and
- (c) High power 40× of nodule of mixed small and large B cell phenotype.

Table 3. Case 3 Immunohistochemistry (DAKO Antibodies).

Immunohistochemistry Panel				
Antibodies	Specificity	Results		
Anubodies		Follicular Area	Diffuse Area	
LCA	Leucocytes common antigen	+	+	
CD45RA	B-cell	+	+	
CD20	B-cell	+	+	
CD5, CD45RO	T-cells	_		
AntiC Clin D1	Cyclin D1	_		
Myeloperoxidase		_		
Alkaline Protein		-	-	
Bcl2	FCC	_	_	

NHL = Non-Hodgkin's Lymphoma

HL RSC = Hodgkin's Lymphoma Reed-Sternberg Cells

FCC = Follicular Center Cells

The case was diagnosed as composite NHL of diffuse large B-cell lymphoma in a background of FCCL of mixed small and large cell, intermediate grade.

Case 4

A fifty-four-year-old female who was presented with difficulty of swallowing associated with vomiting for long duration. On examination, she had enlarged right and left tonsils. The patient was admitted for a tonsillectomy. Both right- and left-tonsils were excised. The left one measuring $2.5 \times 2 \times 2$ cm, and the entire right tonsil was also excised measuring $3 \times 2.5 \times 2$ cm. A nasopharyngeal biopsy was also obtained. Both right and left tonsils showed white firm tonsils with homogenous cross section. Immunohistochemistry were performed on both tonsils (Fig. 4a-c) and results are presented in Table 4.

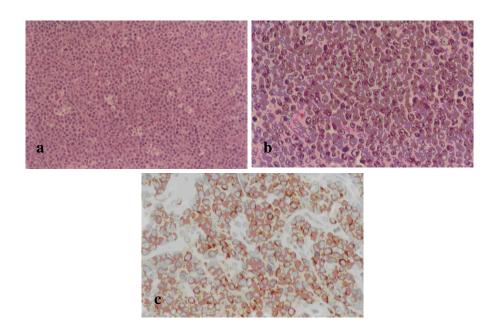


Fig. 4. (a) Low power ($40\times$). To demonstrate the starry sky pattern in the SNC NB lymphoma.

- (b) High power 400× to demonstrate the nuclear features of SNC NB.
- (c) High power $400\times$ with Bcl-2 in the low grade area of small cleaved lymphoma.

Table 4. Case 4 Immunohistochemistry (DAKO Antibodies).

Immunohistochemistry Panel				
	Specificity	Results		
Antibodies		Diffuse Small Non Cleaved Area (Non Burkitt's)	Diffuse Small Cell Area (FCC)	
LCA	Leucocytes common antigen	+	+	
CD45RA	B-cell	+	+	
CD20	B-cell	+	+	
CD5, CD45RO	T-cells	-	_	
CD79	B-cell	+	+	
Kappa	Immunoglobulin	-	-	
Lambda	Immunoglobulin	_	-	
Bcl2	FCC	+	+	
P53	Tumor suppressor gene	+	+	

NHL = Non-Hodgkin's Lymphoma FCC = Follicular Center Cells The diagnosis of tonsils was composite NHL, diffuse small non cleaved (non Burkitt's type) high grade and nodular predominantly small cell, B-cell phenotype of low grade follicular center cells.

Discussion

CL represents two morphological distinct types of lymphomas occurring in one lymph node. These morphological types could be of the same lineage as B-cell lymphoma sub types, or T cell, or it could be a rare combination of B and T. In addition, CL could represent presence of both Hodgkin's lymphoma and NHL in the same lymph node.

Literature review revealed scattered single reports of composite lymphoma, majority of them are distinct types of NHL. Tsang et al. [5] presented a case of CL of follicular center cells (FCC) and mantle cell lymphoma (MCL). They reported a 70-year-old female who had long standing FCCL, low grade, who subsequently developed in the same lymph node foci of persistent FCC in addition to MCL. These components of FCC and MCL were proven by immunohistochemistry and molecular genetic analysis. Fend et al. [6] also reported 3 cases of composite low grade B-cell lymphoma combined with FCC and MCL. They confirmed the diagnosis by molecular genetic analysis. They used the laser capture microdissection technique to isolate the 2 different lymphoma areas. All three lymphomas had 2 separate clones, which included immunoglobulin heavy chain gene (IgH) and Bcl-2 gene rearrangement in the FCC. Zamo et al. [7] also described the third case of MCL and FCCL. They confirmed it immunohistochemical and molecular studies to define biclonal nature of neoplasm. Thev used both manual and LASER-capture microdissection combined to multiple molecular approaches for clonality including detection of heavy and determination. sequence analysis. By immunohistochemistry recombination Fluorescence in-situ Hybridization (FISH), they confirmed the presence of two distinct lymphoma types characterized by specific translocations [namely, t(11:14) and t(14:18)], while they demonstrated two distinct and not clonally related cell populations by molecular techniques. The light chain approach, and particularly the kappa and kappa/Kde recombination detection, proved very useful for solving the clonality issue^[7]. Cachia et al. [8] reported composite MCL and plasmacytoma. The lymph node

showed both MCL was proven by immunohistochemistry and molecular genetic analysis as well as plasmacytoma although these lymphomas are of B-cell lineage yet, morphologically and immunohistochemically are distinct.

From these scattered reports, it seems that the histological progression in B-lineage lymphoma is most evident in patients whose initial biopsies show features of low grade lymphoma, *e.g.*, MCL, FCCL, or diffuse small lymphocyte, follicular small cleaved, or follicular mixed small cleaved and large cell lymphoma. The incidence of progression in pattern or cell type in follicular lymphoma is different in the literature. It accounts up to 80% in autopsy series compared to 40% from biopsy series or relapses that occurred within 5 months of the initial presentation^[9]. Some reports presenting data obtained from staging laboratory showed 5% of patients with low grade follicular lymphoma affecting peripheral sites have unsuspected large cell lymphoma in abdominal site and 10% of patients with large cell lymphoma affecting peripheral site have follicular lymphoma in abdominal sites^[9]. The management of this lymphoma depends on histology of the high-grade component present in the biopsy.

There are a few reports in the literature of CL Hodgkin's and NHL. Miettiner et al. described a case of diffuse large cell lymphoma and nodular form of Lymphocytic Predominant Hodgkin's lymphoma (NLPHD)^[10,11]. They retrospectively reviewed 51 cases with a follow-up for 5 years, a majority of the cases represent CL of large cell and NLPHD. Similar reports in the literature are present. This form of CL of large cell and NLPHD brought up the suggestion of tumor progression, The long follow-up reports of NLPHD that or evolution of NLPHD. evolve to large cell lymphoma, B-cell lineage, support the theory of Bfindings were lineage of NLPHD. Such supported by immunohistochemistry of RS cell in NLPHD that stain positive with Bcell markers^[12-14]. Although there is a heterogeneous expression of the diffuse form of NLPHD with B-cell markers^[15,16]. Yet, 100 percent of cases of NLPHD have B-cell phenotype^[14]. The largest series in the literature of CLHD and NHL is reported by Gonzalez et al. [17], they presented nine cases with 11 subsequent lymph node biopsies, two of the cases had subsequent recurrence of the same type of CL (See Table 5).

Table 5. Gonzalez et al. (17) results.

Hodgkin's & Non-Hodgkin's Combination			
NHL Diagnosis (%)	HD Diagnosis (%)		
Large Cell Immunoblastic (75%)	Nodular Sclerosis (25%)		
Follicular & Diffuse Large Cell (NA)	Unclassified (NA)		
Diffuse Large Cell (90%)	Nodular Sclerosis (10%)		
Diffuse Large Cell (90%)	Mixed Cellularity (10%)		
Follicular & Diffuse Large Cell (50%)	Nodular Sclerosis (50%)		
Large Cell Immunoblastic (75%)	Mixed Cellularity (25%)		
Diff. Mixed Small & Large Cell (95%)	Unclassified (5%)		
Diffuse Large Cell (50%)	Nodular Sclerosis (50%)		
Follicular Mixed Small Cleaved & Large Cell (75%)	Nodular Sclerosis (25%)		
Follicular Mixed Small Cleaved & Large Cell (90%)	Interfollicular (10%)		
Lymphocytic Lymphoma of Intermediate Differentiation (90%)	Mixed cellularity (10%)		

Recent molecular studies contradict the possible link between follicular lymphoma and Hodgkin's disease. In one report by Stetler-Stevenson *et al.* ^[18] reported a high incidence of (14:18) in Hodgkin areas by using polymerase chain reaction (PCR). In another study by LeBrun *et al.* ^[19] reported a lower incidence of (14:18) in Hodgkin's lymphoma. The relationship of Hodgkin's lymphoma and follicular lymphoma, which are the most prevalent lymphoma subtypes, needs further investigation. Their coincidence appears to be more frequent than would be expected on a random basis, and more convincing evidence is required to recognize the progenitor cells.

Small non cleaved-cell, non-Burkitt's lymphoma is often present as peripheral lymph node involvement. Waldeyer's ring and bone marrow may be more frequently involved by small non cleaved-cell, non-Burkitt's lymphoma^[20,21]. Takimoto *et al.* ^[22] reported a case of follicular low grade lymphoma that underwent transformation into high grade lymphoma small non cleaved. They proposed in their report the initial development of the low grade lymphoma is due to rearrangement of Bcl-2 gene, and then there is mutation in P53 (tumor suppressor gene) and rearrangement of C-myc gene which are both found in the high grade small non cleaved-cell, non-Burkitt's lymphoma. These molecular

changes in the lymphoma were the initiator of the transformation of low grade to high grade.

T-cell lymphoma following chemotherapy for Hodgkin's lymphoma has been reported, but synchronous composite occurrence of both lesions is very rare. Sanchez *et al.* ^[23] reported a rare association of combined Hodgkin's lymphoma and T-cell lymphoma in a 65-year-old black man. The patient presented with diffuse lymphadenopathy, fever, weight loss, and night sweats. Subsequent biopsy of an auxiliary lymph node revealed a CL composed of classic Hodgkin's lymphoma and a peripheral T-cell lymphoma. A needle biopsy of the liver also showed involvement by the CL. In situ hybridization studies revealed positive Epstein-Barr virus (EBV) in RSC^[23].

In Case 4, it is believed that there is initially the low grade small cleaved which underwent mutation in P53 that converts it into higher grade small non cleaved-cell, non-Burkitt's lymphoma. Presence of Bcl-2 gene rearrangement in the low grade component is supportive of the origin of this small cleaved is from follicular center of the lymphoid follicles of the tonsils as the lymph node FCCL. On the other hand, presence of small non cleaved-cell, non-Burkitt's lymphoma which shows positive Bcl2 gene rearrangement by immunohistochemistry is keeping with Yano et al. [24] who reported on the pattern of Bcl-2 gene rearrangement. His reported conclusions were that small non cleavedcell, non-Burkitt's lymphoma has a heterogenous expression of Bcl-2. In one group, the patient presented with extranodal disease and the origin of neoplastic cells was not established. The other group expressed Bcl-2 gene rearrangement and the patient presented with peripheral lymphadenopathy and the cell of origin of the neoplasm was follicular center cell.

In conclusion, CL is not common and it needs meticulous examination of the lymph node or lymphoid tissue to avoid missing its diagnosis. Immunohistochemistry, cytogenetics, and molecular genetics with different techniques could help in making specific diagnostic entities. The therapy of this form of lymphoma is towards the high grade component in its histology^[11,13].

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الورم اللمفاوي المركب

فدوى جميل ألطف و جودت أحمد المغربي قسم الأمراض، كلية الطب، جامعة الملك عبدالعزيز، جدة المملكة العربية السعودية

المستخلص. الورم اللمفاوي المركب هو ورم نادر الحدوث في الأنسجة اللمفاوية، و في هذه الدراسة قمنا بإعطاء فكرة عن أربع حالات شخصت كورم لمفاوي مركب في حياتنا الطبية العملية: اثنتان من هذه الحالات شخصتا في سيدات، وأول ما أكتشف بواسطة ظهور ورم أو تضخم في منطقة الغدد اللمفاوية أسفل البطن وفي الرقبة، أما الحالتان الثالثة والرابعة فشخصتا عند سيدة وعند رجل في منطقة اللوزين، أعمار هؤلاء المرضى تراوحت ما بين ٢٥-٤٥ سنة. التشخيص كان عن طريق الموبق المناعية.

وتم تشخيص الحالتين الأولى والثانية بالورم اللمفاوي من نوع هودجكن المركب مع الورم اللمفاوي غير هودجكن، أما الحالتين الثالثة والرابعة فهما عبارة عن صورتين مختلفتين من الأورام اللمفاوية غير هودجكن.

كما تم في هذه الدراسة عرض مفصل للحالات التي صادفناها وبحثنا في الأدبيات المنشورة سابقاً عن الحالات المماثلة.