

## Composite diffuse large B-cell lymphoma and classical Hodgkin's lymphoma of the stomach: Case report and literature review

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### Abstract

The combination of classical Hodgkin's lymphoma (cHL) and non-Hodgkin lymphoma coexisting in the same patient is not common, especially in one extranodal location. Here we present a rare case of composite diffuse large B-cell lymphoma (DLBCL) and cHL occurring simultaneously in the stomach of a 53-year-old female who presented with upper abdominal discomfort and gas pain. Surgery was performed and the disease was diagnosed pathologically as composite lymphoma of DLBCL and cHL using hematoxylin-eosin and immunohistochemical staining. Epstein-Barr virus (EBV) infection was not detected by *in situ* hybridization for EBV-encoded RNA or immunohistochemistry for EBV latent membrane protein-1. Polymerase chain reaction analysis from the two distinct components of the tumor demonstrated clonal immunoglobulin  $\kappa$  light chain gene rearrangements. The patient died approximately 11 mo after diagnosis in spite of receiving eight courses of the CHOP and two courses of the rituximab-CHOP (RCHOP)

chemotherapy regimen. This case report showed that the two distinct components, DLBCL and cHL, appeared to originate from the same clonal progenitor cell, and that EBV infection was not essential for transformation during the course of tumorigenesis.

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**Key words:** Composite lymphoma; Diffuse large B-cell lymphoma; Hodgkin's lymphoma; Stomach

**Core tip:** Classical Hodgkin's lymphoma (cHL) commonly manifests in lymph nodes whereas primary extranodal cHL in the gastrointestinal tract is very rare, and only single cases of primary gastric cHL have been reported in the literature. The combination of cHL and non-Hodgkin lymphoma (NHL) coexisting in the same patient is not common, especially in one extranodal location. The combination of cHL and NHL coexisting in the stomach is extremely rare. Here we present a case of composite diffuse large B-cell lymphoma and mixed cellularity cHL involving the stomach, and present a review of the literature.

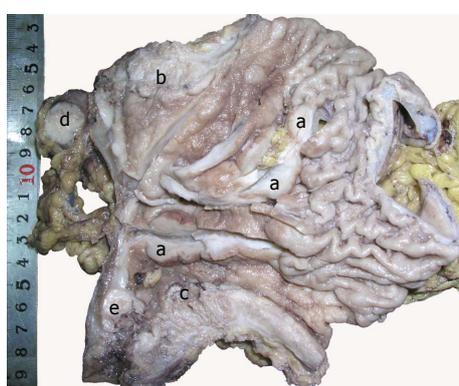
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### INTRODUCTION

Composite lymphoma (CL), which is defined as the coexistence of two or more morphologically and phenotypically distinct lymphoma types in a single anatomic organ or tissue, is unusual<sup>[1]</sup>. Almost all the primary stomach



**Figure 1** Gastroscopy showing an irregular ulcer covered with white exudates (A) and multiple mucosal nodularities in the gastric corpus (B) and a circular ulcer in the gastric pyloric canal (C).



**Figure 2** Macroscopic findings of the lesions. Multiple mucosal nodularities (a) and an ulcer (b) in the gastric corpus, a circular ulcer in the gastric pyloric canal (c), perigastric (d) and parapyloric (e) swollen lymph nodes.

lymphomas are non-Hodgkin's lymphoma (NHL), the majority of which are of B-cell origin, and mucosa-associated lymphoid tissue lymphoma and diffuse large B-cell lymphoma (DLBCL) account for over 90%<sup>[2]</sup>. Classical Hodgkin's lymphoma (cHL) commonly manifests in lymph nodes whereas primary extranodal cHL in the gastrointestinal tract is very rare, estimated at 0.025% of all cHL, and only single cases of primary gastric cHL have been reported in the literature<sup>[3]</sup>. The combination of cHL and NHL coexisting in the stomach is extremely rare. Here we present a rare case of composite DLBCL and mixed cellularity cHL involving the stomach, and present a review of the literature.

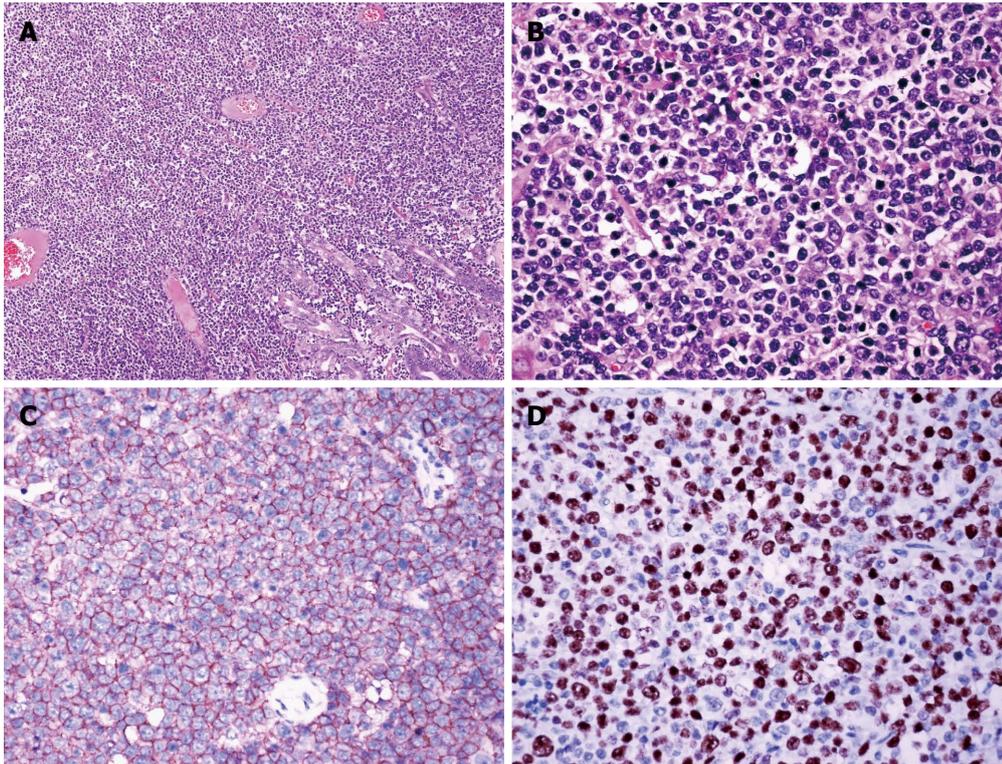
## CASE REPORT

A 53-year-old female presented with upper abdominal discomfort and flatulent pain for over an 8-mo period and her condition became gradually worse. She also described a substantial weight loss and anorexia over the preceding 6 mo. Computed tomography (CT) scans of the abdomen showed thickening of the wall in the gastric pylorus and gastric corpus, and uneven enhancement could be seen after intravenous administration of contrast agent. Gastroscopy revealed an irregular ulcer

covered with white exudates (Figure 1A) and multiple mucosal nodularities in the gastric corpus (Figure 1B). Another circular ulcer covered with white exudates and effusion was simultaneously found in the gastric pyloric canal (Figure 1C). Biopsy specimens were obtained from the two ulcers. A histologic diagnosis of small round cell malignant tumor, indicating lymphoma, was made. Routine blood examination showed hemoglobin 115 g/L, white blood cell count  $5.32 \times 10^9/L$ , neutrophils 52.3%, lymphocytes 19.6%, monocytes 12.1%. Serological testing demonstrated negativity for hepatitis B virus and human immunodeficiency virus infections. The lactate dehydrogenase level (185 U/L) was in the normal range. Abdominal ultrasonography and computed tomography scans of the chest did not show any other abnormalities. No superficial lymphadenopathy was noted.

The patient underwent distal stomach resection because of aggravated symptoms of obstruction. Grossly, the greater and lesser curvatures of the resected stomach measured 17.0 and 7.5 cm respectively. The gastric wall was diffusely thickened and multiple different sizes of mucosal nodularities ranging from 1 cm to 2.5 cm in diameter (Figure 2, a) and a well circumscribed ulcer measuring 4 cm  $\times$  3.5 cm  $\times$  0.5 cm (Figure 2, b) were identified in the gastric corpus. The gastric pyloric canal presented with increased thickness and stenosis, and a circular ulcer measuring 3 cm  $\times$  3 cm  $\times$  0.8 cm was also found (Figure 2, c). The cut surface of the neoplastic ulcers and mucosal nodularities were grey and soft. Perigastric (Figure 2, d) and parapyloric (Figure 2, e) swollen lymph nodes were identified. Selected tumor tissues were fixed in formalin and embedded in paraffin and cut into sections then stained with hematoxylin and eosin for routine histology. Additional sections of paraffin-embedded tissue were used for immunohistochemical staining and *in situ* hybridization analysis. Genomic DNA was isolated from CD30<sup>+</sup> Hodgkin and Reed-Sternberg (RS) cells and CD20<sup>+</sup> DLBCL cells by micromanipulation, and polymerase chain reaction (PCR) procedures were performed for analysis of immunoglobulin heavy and  $\kappa$  light chain rearrangements.

Microscopically, there were two morphologically and



**Figure 3** Diffuse large B-cell lymphoma of the stomach. A: Large lymphoid cells diffusely infiltration the gastric corpus wall (HE,  $\times 100$ ); B: Nucleoli and frequent mitotic figures (HE,  $\times 400$ ); C: Neoplastic cells diffusely positive for CD20 (immunoperoxidase stain,  $\times 400$ ); D: Nuclear proliferation rate as assessed by Ki-67 staining was approximately 80% (immunoperoxidase stain,  $\times 400$ ). HE: Hematoxylin and eosin.

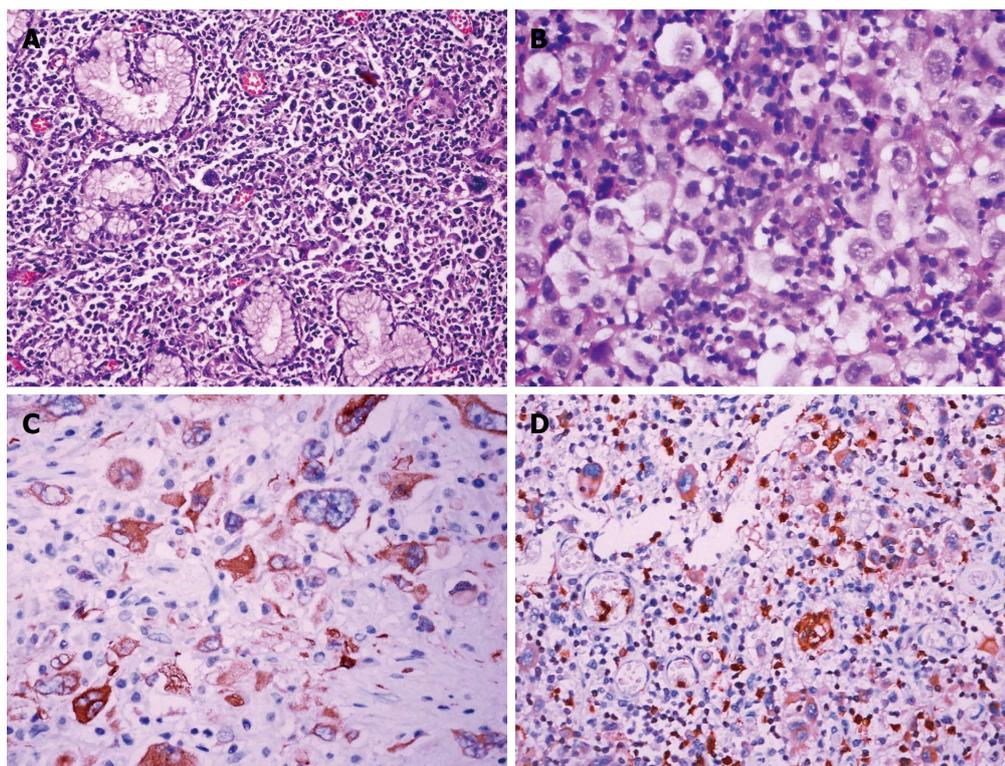
immunophenotypically distinct components in different locations of the stomach. The ulcer and multiple mucosal nodularities in the gastric corpus exhibited a homogeneously uniform population of large lymphoid cells infiltration all layers of the gastric wall (Figure 3A). The nuclei were round or multilobated, with finely dispersed chromatin and evident nucleoli. Frequent mitotic figures were noted (Figure 3B). The neoplastic cells showed uniform expression of CD45, CD20 (Figure 3C), CD79a, Pax-5, MUM1, and absence of CD3, Bcl-6 and CD10. The nuclear proliferation rate as assessed by Ki-67 staining was approximately 80% (Figure 3D). Additional immunohistochemistry displayed tumor cells negative for cytokeratin, CD30, CD15 and other T-cell antigens. The ulcer in the gastric pylorus showed typical mixed lymphocyte, eosinophil granulocyte and neutrophil granulocyte infiltration with fibrosis (Figure 4A), and contained numerous large atypical lymphoid cells, including Hodgkin and RS cells (Figure 4B). The Hodgkin and RS cells were positive for CD30 (Figure 4C), CD15 (Figure 4D), MUM1 and Oct-2, and weakly positive for Pax-5, but negative for CD45, CD20, CD79a, CD3, CD10 and BOB.1. Interestingly, the perigastric and parapyloric swollen lymph nodes were infiltrated by tumor cells of DLBCL and cHL, respectively. Neither cell population showed markers of Epstein-Barr virus (EBV) infection by *in situ* hybridization for EBV-encoded RNA or immunohistochemistry for EBV latent membrane protein-1. On the basis of these morphologic and immunohisto-

chemical characteristics, the pathological diagnosis of composite DLBCL and mixed cellularity cHL was made. PCR analysis from the two distinct components of the tumor demonstrated clonal immunoglobulin  $\kappa$  light chain gene rearrangements (Figure 5).

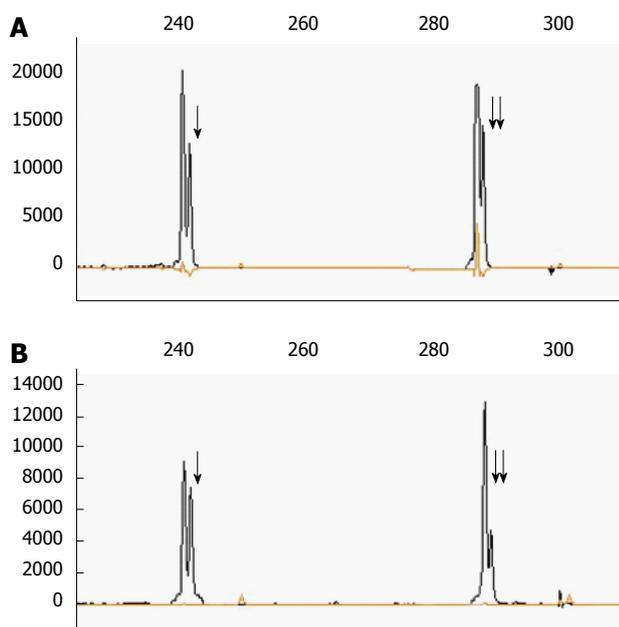
After surgery, the patient was treated with eight courses of a standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy regimen, after which she showed an excellent response with normal brain, thoracic and abdominal CT scans. Unfortunately, repeat CT scans and ultrasonography revealed tumor recurrence with abdominal tumor load 7 mo after chemotherapy. Then the patient received a further two cycles of rituximab-CHOP (RCHOP) chemotherapy. Unfortunately, she died of multiple organ failure due to lymphoma recurrence on the 11<sup>th</sup> postoperative month. An autopsy was not performed.

## DISCUSSION

The concept of CL was first put forward by Custer<sup>[4]</sup> to explain the occurrence of more than one histological type of lymphoma in the same patient. In the study of more than 1000 cases for the International Working Formulation for NHL, the incidence of CL varied between 1% and 4.7%<sup>[5]</sup>. cHL and NHL are morphologically and clinically distinct neoplasms. The combination of cHL and NHL coexisting in the same tissue is rare and much more uncommon than other combinations<sup>[3]</sup>. According



**Figure 4 Classical Hodgkin's lymphoma of the stomach.** A: Mixed lymphocyte, eosinophil granulocyte and neutrophil granulocyte infiltrating the gastric pyloric canal wall (HE,  $\times 200$ ); B: Hodgkin and Reed-Sternberg (RS) cells are present (HE,  $\times 400$ ); C, D: Hodgkin and RS cells positive for CD30 and CD15, respectively (immunoperoxidase stain,  $\times 400$ ). HE: Hematoxylin and eosin.



**Figure 5 Polymerase chain reaction analysis from the two distinct components of the tumor demonstrated clonal immunoglobulin  $\kappa$  light chain gene rearrangements.** The asterisks indicate two peaks representing the rearranged polymerase chain reaction products from position 241 bp (arrow) and 281 bp (double arrows) regions of immunoglobulin  $\kappa$  light chain gene, respectively. A: DNA from the dissected diffuse large B-cell lymphoma component. B: DNA from the dissected classical Hodgkin lymphoma component.

to our literature review, a total of 10 cases, including the present case, reported a combination of DLBCL and cHL within the same site simultaneously<sup>[6-13]</sup>. The clinical data of all previously published cases of composite DLBCL and cHL are listed in Table 1. In these cases, there were five cases of combination of DLBCL and cHL in the lymph nodes, three cases in the stomach, one case in the small intestine and one case in the anterior mediastinum, indicating that the gastrointestinal tract is the most common extranodal site involved in this kind of composite lymphoma. Prochorec-Sobieszek *et al*<sup>[9]</sup> firstly reported localized gastric DLBCL and cHL as secondary neoplasms in two patients with chronic lymphocytic leukemia. To the best of our knowledge, this is the first case report of composite DLBCL and cHL coexisting in the stomach with no history of lymphoma or leukemia.

The pathogenesis of CL is inconclusive. Viral infections, genetic susceptibility, genetic mutations, and immune suppression are CL pathogenic factors. However, no single definite mechanism has been proposed to explain the pathogenesis of different types of CL as the etiology is variable, complex and differs according to the types of lymphomas involved<sup>[14-16]</sup>. In general, cHL is associated with EBV; on the other hand, NHL is infrequently associated with EBV. When cHL and NHL are present in the same anatomic site, there is a higher correlation with the presence of EBV in both lymphoma

**Table 1 Composite diffuse large B-cell lymphoma and classical Hodgkin's lymphoma: A review of the literature**

Ref.	Gender/age (yr)	Organ	EBV infection	Treatment	Follow up time	Status
Paulli <i>et al</i> <sup>[6]</sup>	Male/37	Supra-clavicular lymph nodes	NA	8 cycles of pro-MACE-CytaBOM chemotherapy	23 wk	ANED
Bellan <i>et al</i> <sup>[7]</sup>	Female/29	Cervical lymph nodes	NA	MACOP-B chemotherapy for 8 wk and autologous stem cells transplant	30 mo	ANED
Rosenquist <i>et al</i> <sup>[8]</sup>	Female/74	Inguinal lymph nodes	+	6 cycles of CHOP chemotherapy	12 wk	ANED
Prochorec-Sobieszek <i>et al</i> <sup>[9]</sup>	Male/67	Stomach	+	6 courses of CHOP chemotherapy	22 wk	ANED
	Male/76	Stomach	+	6 courses of cyclophosphamide and cladribine chemotherapy	14 wk	DOD
Huang <i>et al</i> <sup>[10]</sup>	Male/56	Small intestine	+	Lesion resected	6 d	DOD
Miyagaki <i>et al</i> <sup>[11]</sup>	Male/75	Axillary lymph nodes	+	6 courses of RCHOP chemotherapy	3 yr	DOD
Yu <i>et al</i> <sup>[12]</sup>	Female/37	Anterior mediastinum	-	6 courses of CHOP chemotherapy and 23 times radiotherapy	33 wk	ANED
Bautista-Quach <i>et al</i> <sup>[13]</sup>	Female/6	Multiple lymph nodes	+	Combined chemotherapy (program unknown)	17 wk	DOD
Wang <i>et al</i> (present case)	Female/53	Stomach	-	Lesion resected and 8 courses of CHOP and 2 courses of RCHOP chemotherapy	45 wk	DOD

NA: Not available; +: Positive; -: Negative; CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone; RCHOP: Rituximab-CHOP; ANED: Alive with no evidence of disease; DOD: Died of disease.

cells than when two lymphomas occur at different times and/or at different sites. If the two components demonstrate positivity for EBV, it would be suggested that a commonly infected progenitor cell might be responsible for both lymphomas<sup>[17,18]</sup>. From assessment of the data in Table 1, composite DLBCL and cHL often showed EBV positivity, suggesting an origin from a commonly EBV-infected progenitor cell; however, two components from two cases including our patient were all negative for EBV, indicating EBV infection did not seem to be the primary event in this tumorigenesis.

Lymphoma, generally, is defined as monoclonal proliferation of lymphocytes (T cell, B cell or natural killer cell). Coexistence of DLBCL and cHL in the same anatomic location has been reported occasionally; studies using molecular techniques have proved that they may be clonally related (*i.e.*, derived from the same lymphoid progenitors) or not related (*i.e.*, different lymphoid progenitors)<sup>[7-10]</sup>. Controversy about this issue may reflect the lack of a full understanding of the pathogenesis of these lymphomas or the heterogeneity of Hodgkin lymphoma and NHL. In the present case, identical immunoglobulin  $\kappa$  light chain gene rearrangements were seen in the two distinct components, indicating that both components, despite their distinctly different morphologic features and immunophenotype, were indeed derived from the same clone. Thus, DLBCL and cHL coexisting in the stomach in our case can be considered a true CL with two distinctive presentations.

The pathological differential diagnosis of composite DLBCL and cHL in the present case mainly included cHL transformation to DLBCL, anaplastic variant of DLBCL, T cell/histiocyte-rich large B-cell lymphoma (THRLBCL), anaplastic large cell lymphoma (ALCL) and grey zone lymphoma. The characteristic morphology and immunophenotype of the tumor cells in conjunction with clinical features aid in the differential diagnosis. cHL

transformation to DLBCL may be differentiated from the current case as the two distinct lymphoma occurred simultaneously within different sites of the stomach without a histological mixing zone. An anaplastic variant of DLBCL is characterized by large tumor cells with bizarre pleomorphic nuclei that may resemble Hodgkin and/or RS cells, and it may be differentiated according to its consistent immunological staining for B-cell markers, such as CD20 and CD79. THRLBCL is comprised of scattered, single, large B cells embedded in a background of T cells and a variable number of histiocytes. These large B cells may mimic Hodgkin and RS cells in cHL, but they express pan B-cell markers with no expression of CD15 and CD30. The "Hodgkin-like pattern" accounts for 3% of ALCL cases, which is characterized by morphological features mimicking nodular sclerosing cHL. CD15 expression is rarely observed and when present only a small proportion of the neoplastic cells are stained; however, Hodgkin and RS cells in cHL are always weakly positive for Pax-5, which is different from ALCL. The most presentation of grey zone lymphoma is a large anterior mediastinal mass with rare involvement of non-lymphoid organs. Some areas may more closely resemble DLBCL and others appear more like cHL. In cases that morphologically resemble cHL, uniform strong expression of CD20 and other B-cell markers and absence of CD15 would favor the diagnosis of grey zone lymphoma. Other histological differential diagnoses, including leukocytopenia, poorly differentiated carcinoma, sarcoma, reactive lymphoid proliferation and collision tumor should be cautiously considered<sup>[19]</sup>.

To conclude, we report a rare case of composite DLBCL and cHL involving the stomach and describe the histologic and immunophenotypic findings. The contribution of immunohistochemistry plays an important role in differential diagnosis. Using molecular techniques, we further proved that the two different components ap-

peared to originate from the same clonal progenitor cell, and that EBV infection was not essential for transformation during the course of tumorigenesis.

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