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ORIGINAL ARTICLE

Primary sinonasal large B cell lymphoma is as histopathologically heterogeneous as systemic large B cell lymphoma but may show subtype-specific tropism for specific sinonasal anatomic sites

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Abstract

Large B cell lymphomas (LBCL) are a heterogeneous group of diseases with variable presentations and prognoses. Rarely, LBCLs arise in the sinonasal tract and are distinct from extranodal NK/T-cell lymphoma which is more typical in this anatomic location. We hypothesized that large B cell lymphoma primary to the sinonasal tract (snLBCL) would be heterogeneous and include high-grade B cell lymphomas (HGBCL) described in the revised 4th edition WHO classification of lymphomas. We retrospectively evaluated cases of snLBCL at our center, and performed additional immunohistochemical and in situ hybridization studies where needed for modern WHO classification. Our cohort consisted of 25 cases, 15 males and 10 female patients, aged 14 to 87 years, with predominantly nasopharyngeal disease ($n=11$), Ann Arbor stage IIE ($n=15$), and immunocompetence ($n=24$). According to revised 2016 WHO criteria, 20 of the 25 cases were DLBCL-NOS (80%, two-thirds germinal center phenotype), 3 were HGBCL-NOS (8%, one with *MYC* rearrangement without *BCL2* rearrangement), and 2 were EBV-LBCL (8%). Among DLBCL-NOS, those arising in the nasopharynx all showed a germinal center B cell (GCB) phenotype, whereas both evaluable maxillary sinus tumors showed non-GCB characteristics ($p=0.02$). These data show that large B cell lymphoma primary to the sinonasal tract is histopathologically heterogeneous as systemic large B cell lymphoma. The observation that GCB and non-GCB tumors differs in anatomic location suggests that microenvironmental factors in sinonasal anatomic sites may drive lymphoma characteristics.

Keywords Diffuse large B cell lymphoma · High-grade B cell lymphoma · Sinonasal tract · Head and neck lymphoma

Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma worldwide [1–3]. There are numerous clinicopathologic subtypes of DLBCL which have variable pathobiology, prognosis, and therapeutic approaches. Although many large B cell lymphomas arise in lymph nodes, subtypes arising in specific extranodal sites often harbor stereotyped clinicopathologic and prognostic features [4, 5]. Unique genetic and molecular alterations have been identified to underlie large B cell lymphomas primary to the central nervous system (primary CNS lymphoma), anterior mediastinum/thymus (primary mediastinal large B cell lymphoma), and skin/subcutis (DLBCL, leg type), to name a few [6–9]. Additionally, the revised 2016 World Health Organization classification of lymphoid neoplasms introduced nomenclature to distinguish between DLBCL, not otherwise specified (DLBCL-NOS) from cases with

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potentially more aggressive behavior: high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (so-called double and triple-hit lymphomas; HGBCL-D/TH) and, in the absence of these rearrangements, high-grade B cell lymphoma, not otherwise specified (HGBCL-NOS; cases with morphologic and other features of the former WHO category of B cell lymphoma, not otherwise specified, with features intermediate between diffuse large B cell lymphoma and Burkitt lymphoma) and/or blastoid morphologic features [10].

With an estimated annual incidence in the Western population of 0.08–0.17 cases per 100,000, the prevalence of DLBCL presenting in the sinonasal tract represents a small percentage of all non-Hodgkin lymphoma (19.4 cases per 100,000) [11–13]. The implications of primary presentation of large B cell lymphoma in the sinonasal tract are uncertain.

The primary aim of this study was to define clinicopathologic characteristics of large B cell lymphomas primary to the sinonasal tract (sinonasal large B cell lymphoma, or snLBCL) in light of the revised 2016 WHO classification of lymphoid neoplasms. Based on clinical experience with challenging patients, we hypothesized that snLBCL are enriched for aggressive forms of large B cell lymphoma as defined by 2016 WHO criteria compared to systemic counterparts.

Materials and methods

Electronic records of the Department of Pathology at Vanderbilt University Medical Center, including from Monroe Carell Jr. Children's Hospital at Vanderbilt, were queried for cases of large B cell lymphoma involving the nasal cavity, paranasal sinuses, or nasopharynx from January 1, 1990 to July 1, 2017 following Institutional Review Board (IRB) approval. "Large B cell lymphoma" was defined as WHO diagnoses of diffuse large B cell lymphoma NOS (DLBCL NOS), high-grade B cell lymphoma NOS (HGBCL NOS), high-grade B cell lymphoma with *C-MYC* and *BCL2* and/or *BCL6* rearrangements (double hit B cell lymphoma, or HGBCL-D/TH), or EBV + large B cell lymphoma NOS (EBV-LBCL). Records from a total of 49 cases were identified and reviewed. Cases were excluded if key clinical data and/or formalin-fixed paraffin-embedded (FFPE) tissue blocks were unavailable, precluding revised 4th edition WHO classification ($n=18$); if clinical history showed disease previously or concurrently involving other systemic site(s) considered to be the primary site of disease ($n=3$); or if the case represented a repeat biopsy from the same patient ($n=2$).

Patient medical records were reviewed for clinical, treatment, and outcome information. Immunohistochemistry (IHC) and in situ hybridization (ISH) results reported in original pathology reports from pre-treatment biopsy specimens were recorded. Additional studies were performed on subsets of the snLBCL cases as needed to render a WHO subclassification; additional studies performed as part of this prospective evaluation included cell-of-origin classification per the Hans cell-of-origin (COO) classifier (CD10, BCL6, and MUM1 IHC, $n=19$) [14], EBER ISH (EBV-encoded RNA, $n=5$), and *MYC*, *BCL2*, and *BCL6* fluorescence ISH (FISH; $n=5$, 5, and 8, respectively), and "double-expressor" phenotype by IHC, [defined as dual MYC ($\geq 40\%$ of lymphoma cells) and BCL2 ($\geq 50\%$) protein expression; $n=13$ and 10, respectively) [15, 16].

CD10, BCL6, MUM1, BCL2, and C-MYC IHC and EBER ISH were performed as follows: 5-µm FFPE slides were placed on a Leica Bond Max IHC stainer, and all steps were performed on a Leica Bond Max (Buffalo Grove, IL). Slides were deparaffinized. For IHC, heat-induced antigen retrieval was performed using the Epitope Retrieval 2 solution (Leica Bond Max) for 20 min; for EBER ISH, enzyme retrieval was performed using Proteinase K (Dako, Santa Clara, CA) for 5 min. Sections were incubated with Ready-To-Use anti-CD10 (PA0270), anti-BCL6 (PA0204), anti-MUM1 (PA0129), or anti-BCL2 (PA0129) (Leica); anti-cMYC (ab32072; Abcam Laboratories, Cambridge, MA) diluted 1:600 for 1 h; or hybridized with the Ready-To-Use EBER probe (Leica) for 2 h and placed in anti-Fluorescein antibody (Leica) for 15 min. The Bond Polymer Refine detection system (Leica) was used for visualization. Slides were then dehydrated, cleared and cover-slipped.

For FISH studies, FFPE sections with areas of tumor marked by a pathologist were processed according to standard laboratory procedures. Briefly, slides were baked at 90 °C for 1 h, followed by deparaffinization steps that include treatment with protease and pretreatment buffers and subsequent hybridization with the dual-color break-apart probes for *BCL6* and *MYC* and a dual-color dual-fusion translocation probe for *IGH*/*BCL2* (Abbott Molecular, Des Plaines, IL). At least 200 cells were analyzed for each probe, with a minimum of two images per probe per case.

Fisher's exact test was used to compare categorical data, with p-values less than 0.05 considered statistically significant.

Results

Twenty-five (25) cases of LBCL primary to the sinonasal tract were included in the study (Table 1). This included 15 male and 10 female patients aged 14 to 87 years at diagnosis (mean age 61.5 years; median age 67.4 years). Primary sites of disease included nasopharynx ($n=13$), nasal cavity (8), and maxillary sinus (4). The Ann Arbor stage at diagnosis in a majority of patients was IIE ($n=15$), an extranodal mass

Table 1 Characteristics of sinonasal large B cell cohort ($n=25$)

Case	WHO diagnosis	Age (years)	Sex	Primary site	Stage	IPI	COO	DE	Necrosis	CD30	CD5	Ki67	Treatment	Follow-up (years)	Outcome
1	DLBCL-NOS	87.5	F	Nasopharynx	II	NA	GCB	Yes	No	(+)	(-)	90	None	1.3	DOD
2	DLBCL-NOS	23.0	M	Nasopharynx	IE	0	GCB	No	No	NA	(-)	70	Chemo	1.8	CR
3	DLBCL-NOS	55.8	F	Nasopharynx	IIA	0	GCB	No	Focal	(+)	(-)	70	Chemo	0.7	CR
4	DLBCL-NOS	47.6	M	Nasopharynx	IIE	1–2	GCB	Yes	Focal	(-)	(+)	80	Chemoradiation	1.6	DOD
5	DLBCL-NOS	58.1	F	Nasopharynx	IV	NA	GCB	No	No	NA	(-)	NA	Chemoradiation + auto-HSCT	7.0	AWPD
6	DLBCL-NOS	49.7	M	Nasopharynx	II	0	GCB	No	No	(-)	(-)	25	Chemoradiation	7.4	CR
7	DLBCL-NOS	64.8	F	Nasopharynx	II	2	GCB	No	No	(+)	(-)	70	Chemo	4.0	CR
8	DLBCL-NOS	70.9	M	Nasopharynx	I	2	GCB	Yes	No	(-)	(-)	80	Chemoradiation	2.9	CR
9	DLBCL-NOS	38.0	M	Nasopharynx	IIE	2	GCB	No	Extensive	(-)	(-)	85	Chemo	5.9	CR
10	DLBCL-NOS	14.1	M	Nasopharynx	IV	NA	NA	No	No	NA	(-)	NR	Chemo	2.3	CR
11	DLBCL-NOS	73.6	M	Maxillary sinus	I	1	Non-GCB	No	Yes	NA	(-)	40	Chemoradiation	2.5	CR
12	DLBCL-NOS	74.0	M	Maxillary sinus	I	1	NA	NA	Yes	NA	NA	90	NA	NA	NA
13	DLBCL-NOS	40.8	M	Maxillary sinus	I	NA	Non-GCB	NA	No	(-)	(-)	95	Chemoradiation + auto-HSCT	6.2	DOD
14	DLBCL-NOS	62.7	F	Nasal cavity	II	2	Non-GCB	Yes	Focal	(-)	(+)	80	Chemo	9.1	CR
15	DLBCL-NOS	67.9	M	Nasal cavity	IIE	1	Non-GCB	Yes	No	(-)	(-)	85	Chemo	2.4	AWPD
16	DLBCL-NOS	69.7	F	Nasal cavity	II	1–2	Non-GCB	Yes	No	(-)	(-)	95	Chemoradiation	0.5	NA
17	DLBCL-NOS	70.8	M	Nasal cavity	1E	1	GCB	Yes	No	(-)	(-)	100	Chemo	0.7	NA
18	DLBCL-NOS	73.8	F	Nasal cavity	IV	4	Non-GCB	No	No	(-)	(-)	Variable	Chemo	0.1	DOD
19	DLBCL-NOS	81.5	M	Nasal cavity	II	1	GCB	Yes	Focal	(-)	(-)	80	Chemo	0.9	CR
20	DLBCL-NOS	67.4	F	Nasal cavity	IE	1	GCB	Yes	Yes	(-)	(-)	90	Chemoradiation	4.7	CR
21	HGBCL (MYC)	78.8	F	Maxillary sinus	IIA-E	1	Non-GCB	No	No	(-)	(-)	75	Chemo	4.8	DOD
22	HGBCL-NOS	59.1	M	Nasal cavity	IIE	1	GCB	NA	No	NA	(-)	95	Unknown	1.4	DOD
23	HGBCL-NOS	83.3	M	Nasopharynx	II	1	Non-GCB	NA	No	NA	(-)	100	Chemo	0.1	DOD
24	EBV-LBCL	72.5	F	Nasopharynx	IIEA	1	Unknown	NA	No	NA	NA	NA	Chemo	2.6	DOD
25	EBV-LBCL	53.2	M	Nasopharynx	IIB	1	Non-GCB	No	Extensive	(+)	(-)	50	Chemo	1.0	AWPD

WHO World Health Organization, *DLBCL-NOS* diffuse large B cell lymphoma, *HGBCL* high-grade B cell lymphoma not otherwise specified, *EBV-LBCL* EBV-positive large B cell lymphoma, *F* female, *M* male, *IPI* International Prognostic Index score, *NA* not applicable (unknown), *COO* cell of origin classifier by Hans algorithm (CD10, BCL6 and C-MYC immunohistochemistry)[14], *GCB* germinal center B cell phenotype, *DE* double expressor immunophenotype by immunohistochemistry (C-MYC + BCL2)[15,16], *Chemo* chemotherapy, *Chemoradiation* chemotherapy and radiation, *auto-HSCT* autologous hematopoietic stem cell transplant, *DOD* died of disease, *CR* complete remission, *AWPD* alive with progressive disease

with an adjacent involved lymph node group, typically ipsilateral cervical, followed by stage IE (8) and stage IV (2, including one with bone marrow involvement). One patient was known to be human immunodeficiency virus (HIV) positive at the time of diagnosis.

According to revised 2016 WHO criteria, 20 of the 25 cases were DLBCL-NOS (80%), 3 were HGBCL-NOS (8%) by morphology and FISH studies, and 2 were EBV-LBCL (8%) (Fig. 1). (One case of HGBCL had a *MYC* rearrangement without *BCL2* rearrangement; *BCL6* rearrangement status remains unknown, as *BCL6* FISH on archived FFPE failed, and so is classified as HGBCL-NOS for this study.) Among the 20 cases of DLBCL-NOS characterized based on the Hans algorithm classification, 12 cases were GCB subtype while six (6) were non-GCB subtype; insufficient immunohistochemical studies were available in two cases for COO classification. All nasopharyngeal DLBCL-NOS of determined COO were GCB (9 of 9), and both evaluable maxillary sinus DLBCL-NOS were non-GCB (2 of 2), ($p = 0.02$). DLBCL-NOS primary to the nasal cavity included both GCB and non-GCB classifications (4 of each).

Among 18 of the 20 DLBCL-NOS cases where double expressor status could be determined, 9 showed a double expressor phenotype (50%) and 9 were a non-double expressor phenotype (50%). There was a borderline statistically significant trend toward double expressor phenotype in tumors arising in the nasal cavity (6 out of 7) compared to those arising in the nasopharynx (3 out of 10) ($p = 0.05$). Two (2) of 15 evaluable cases of DLBCL-NOS showed diffuse CD30 expression (13%), and a single case expressed CD5 (among 1 of 19 evaluable cases, or 5%). The Ki67 proliferation fraction among DLBCL-NOS varied widely, from 50% to nearly 100%, and 9 of the 20 cases (45%) showed at least focal tumor necrosis. CD30 expression or Ki67 proliferation fraction > 80% were not associated with primary anatomic location (p values > 0.05).

Among the overall cohort, staging bone marrow (BM) biopsy was performed at diagnosis in 16 cases (64%). Concordant disease involvement was diagnosed in one patient (6%) with DLBCL-NOS. One patient (6%) with HGBCL-NOS was found to have bone marrow involvement by chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) during HGBCL-NOS staging; consensus among the treating oncologists was that the CLL/SLL represented discordant/incidental bone marrow disease. Two additional patients (13%), one with DLBCL-NOS and one with HGBCL with *MYC* rearrangement without *BCL2* rearrangement, had small clonal populations detected by immunoglobulin heavy chain gene rearrangement by polymerase chain reaction; however, there was no morphologic or immunophenotypic evidence of marrow involvement by lymphoma. Lumbar puncture for cerebrospinal fluid involvement was performed at diagnosis in 7 patients (28%) and

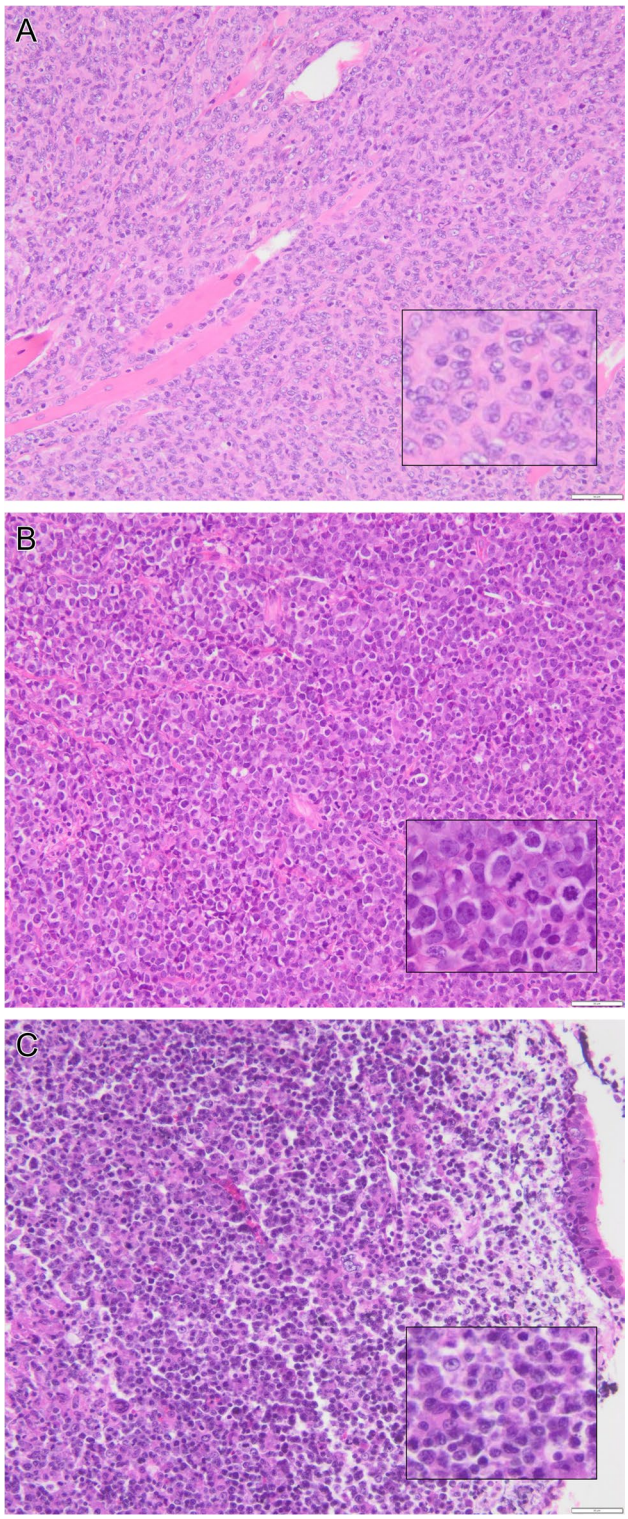

Fig. 1 Representative biopsies of nasopharyngeal mass with distinct WHO classification. **A** Diffuse large B cell lymphoma, not otherwise specified (DLBCL-NOS) with a germinal center B cell immunophenotype from a 23-year-old male (case 2 in Table 1). **B** High-grade B cell lymphoma, not otherwise specified (HGBCL-NOS) from an 83-year-old male (case 23). **C** EBV-positive diffuse large B cell lymphoma, not otherwise specified (EBV-LBCL) from a 53-year-old male (case 25) with overlying sinonasal-type mucosa (upper right). All images: 200× original magnification, insets: 600×

was negative for involvement by lymphoma in all cases. No patients had CNS relapse.

Treatment information was available for 24 patients and included chemotherapy alone ($n=15$, or 62.5%), chemotherapy and radiation ($n=8$, or 33%), and patient election to forego treatment given advanced age and comorbidities ($n=1$, or 4%). Chemotherapy regimens in the majority of patients (20/23, or 87%) included rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) upfront and rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) in cases of relapse. Both patients with EBV-LBCL received CHOP without rituximab (9%). Intrathecal methotrexate was administered in 12 cases (52%). The single pediatric patient in the cohort, a 14-year-old male with DLBCL-NOS received cyclophosphamide, vincristine and prednisone (COP) reduction, with the addition of doxorubicin and high dose methotrexate (COPADM) for induction, and cytarabine and etoposide (CYVE) consolidation. Two patients, a 58-year-old female and 40-year-old male, both with DLBCL-NOS, underwent autologous stem cell transplant at relapse.

Clinical follow up data was available for 22 of 25 patients. Eleven (11) patients (50%), all with DLBCL-NOS, demonstrated a complete response to therapy with a median follow up of 2 years 3 months (range, 8 months–7 years and 5 months). Three patients were alive with progressive disease ($n=3$), including two patients with DLBCL-NOS and one with EBV- LBCL. Eight (8) patients died of disease (36%), including both patients with HGBCL-NOS, one patient with EBV-LBCL, and the patient with HGBCL with *MYC* rearrangement (average of 2 years 2 months from diagnosis; range, 1 month–6 years and 3 month). Among the patients with DLBCL-NOS with available follow up data ($n=17$), 11 were alive without evidence of disease (65%), two were alive with progressive disease (12%), and four died of disease (23%). Primary anatomic location was not associated with clinical outcomes (p values >0.05).

Discussion

Here, we have defined the clinical and pathologic features of patients with snLBCL considering the revised 2016 WHO classification. In keeping with the relative rarity of this entity, over a nearly 30-year period at our single tertiary care institution, we identified 25 evaluable cases. An additional 18 cases were excluded due to lack of available clinical data and/or tissue to complete WHO classification. The majority of our patients were male (M:F 3:2) with a wide age range though patients tended to be older (mean age of 61.5 years; median age 67.4 years). Most patients presented with early-stage disease (I-II; $n=23$ of 25, 92%) and had low risk IPI scores (0–1; $n=14$ of 21, 67%). These clinical findings are similar to that reported in the literature for extranodal LBCL [17, 18].

Extranodal DLBCL in patients with stage I disease, such as that limited to the sinonasal tract, has generally been associated with poor prognosis [5]. Furthermore, extranodal DLBCL is enriched for non-GCB type DLBCL which is associated with a significantly worse prognosis than GCB DLBCL [19–21]. However, the growing body of literature suggests that the anatomic site of extranodal disease itself may be associated with clinical outcome [4, 17, 18]. As such, the WHO has incorporated certain sites as distinct entities, for example, primary CNS DLBCL, primary cutaneous DLBCL, leg type, and intravascular LBCL [10]. The head and neck, including the sinonasal tract, has been identified in some studies as a site with a better prognosis compared to nodal sites [17, 22], while others have reported a poor overall survival (45% at 3 years) despite early stage disease and low risk IPI [18, 23].

Using the revised 4th edition WHO classification, the majority of cases in our cohort met criteria for DLBCL-NOS (20/25 or 80%). Two-thirds of our cases were GCB subtype (12/18 or 67%) and one-third non-GCB subtype (6/18 or 33%) by Hans COO classifier, which is more comparable to systemic DLBCL-NOS than to extranodal DLBCL-NOS overall. Of note, it is reported that DLBCL of Waldeyer's ring (which encompasses the nasopharynx, included in our cohort) is predominantly of GCB type while DLBCL arising in the nasal cavity and paranasal sinuses are almost exclusively non-GCB type [4, 18]. Our cohort supports this existing evidence that non-GCB cases are enriched in paranasal/nasal sites while the GCB cases are concentrated in the nasopharynx, further providing evidence that microenvironmental differences across local sinonasal anatomic site may underlie these differences.

One study of 29 cases of DLBCL arising in the sinonasal tract reported associations with a non-germinal center B cell (non-GCB)-like genetic profile, 1p31 and RGS1 abnormalities, and relatively unfavorable prognosis compared with a large cohort of systemic DLBCL [19]. Other recent studies show that patients with sinonasal tract DLBCL benefit from central nervous system-directed chemotherapy [13] as well as combination chemoradiation [24]. The patients in our cohort received heterogeneous therapy based on multiple clinical factors, making conclusions challenging. Indeed, the findings of Carreras et al. [19] suggest that GCB vs. non-GCB enrichment in that cohort (non-GBC-enriched) versus the current study cohort (GCB-enriched) may underlie the prognostic differences observed. Moreover, the 63-patient cohort in Vähämurto et al. [13], which concluded that CNS-directed therapy as well as rituximab show benefit in sinonasal LBCL, also showed non-GCB predominance (68%). It is challenging to compare anatomic site-specific features between our study cohort and that of Vähämurto

et al.because of our study's small sample size. Nevertheless, Vähämurto et al. also included a heterogenous (non-significant) distribution of primary anatomic sites, including the nasal cavity, paranasal sinus, and nasopharynx, although GCB histologies comprised 47% of paranasal cavity-based cases, somewhat in contrast to Carreras et al. and our cohorts.

Indeed, a limitation of our study overall is the small cohort size, from which treatment and outcome associations with histopathologic subclassification are difficult to draw. In addition, CSF status and bone marrow involvement were not systematically assessed at diagnosis, and as such could not be included in our analyses. The remaining five cases in our cohort consisted of two cases of EBV-LBCL, two cases of HGBCL-NOS, and one case of HGBCL with C-MYC rearrangement without BCL2 and unknown status of BCL6 rearrangement due to tissue limitations. It is worth noting that many of the published studies to date have likely included these HGBCL-D/TH and HGBCL-NOS in their series, whereas separate consideration may be in order.

Another limitation is that lymphomas were not assessed for *IRF4* rearrangements [25]. Large B cell lymphoma with *IRF4* rearrangement (LBCL-*IRF4*) is an uncommon, relatively indolent lymphoma with predilection for Waldeyer's ring and cervical lymph nodes of young adult and pediatric patients [26, 27]. Morphologically, LBCL-*IRF4* may show relatively bland cytologic features compared to many DLBCL-NOS, and immunophenotypically, it often expresses all three markers in the Hans classifier (CD10, BCL6, and MUM1) [25]. Among the 5 cases in our cohort that expressed all three markers, MUM1 expression was patchy and weak, and the cytologic features were pleomorphic, with large nucleoli, such that the overall features were not suggestive of a LBCL-*IRF4* diagnosis. Nevertheless, LBCL-*IRF4* is an important consideration in the work-up of snLBCL given its distinct prognosis, and its behavior further supports the concept that regional microenvironmental factors throughout the sinonasal tract influence lymphoma pathogenesis and behavior.

In summary, our data support the conclusions that large B cell Lymphoma primary to the sinonasal tract (snLBCL) is as histopathologically heterogeneous as systemic large B cell lymphoma. Careful WHO subclassification of LBCL arising in these and other extranodal anatomic locations will further inform understanding of clinicopathologic features as well as treatment and prognostic expectations for patients.

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Author contribution A.E.K., T.S., and N.M.R. designed the study. M.L.D., T.S., A.Y., and A.E.K. gathered the data. A.Y. performed experiments. M.L.D., M.A.T., and A.E.K. performed histopathologic review. D.M., T.S., and N.M.R. confirmed the clinical data. M.L.D. and A.E.K. wrote the manuscript. T.S., A.Y., D.M., M.A.T., and N.M.R. edited the manuscript and agreed to the submitted version.

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Availability of data and material The data are presented in tabular form. Additional details can be furnished upon request.

Code availability Not applicable.

Declarations

Ethics approval Vanderbilt University Medical Center Institutional Review Board (IRB) 171277.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no conflict of interests.

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