Original Contribution

Clinicopathologic characteristics and novel biomarkers of aggressive B-cell lymphomas in the nasopharynx

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ABSTRACT

Background: The most common nasopharyngeal lymphoma in the United States are B-cell non-Hodgkin lymphomas (B-NHL). Relatively little is known about the clinicopathologic features of these cases. In this study, we characterize a bi-institutional cohort of aggressive B-NHL primary to the nasopharyngeal area. We compare and contrast EBV-positive versus EBV-negative cases and evaluate expression of SSTR2, CD30, and PD-L1, potential markers for targeted therapeutics.

Methods and results: We retrieved 53 cases of aggressive B-NHL from the two institutions. Staining was performed for in situ EBV (EBER), CD30, SSTR2 and PD-L1. The response to initial therapy, disease-free interval, and survival at two- and five-year following initial diagnosis were used as primary clinical outcome. Overall, 13 out of 53 cases (23%) were EBV positive. CD30 expression was more frequent in EBV-positive than in EBV-negative cases (4/6 vs 1/17). Seven of 14 (50%) cases tested demonstrated expression of PD-L1 within tumor cells; the two EBV-positive DLBCL tested showed substantial PD-L1 reactivity. Six of 15 (40%) cases tested were positive for SSTR2. The three EBV-positive patients with available outcome data died within one year of diagnosis; in contrast, the EBV-negative cases showed survival rate of 100% (8/8) and 83% (5/6) at two- and five-year follow-up, respectively.

Discussion: The aggressive B-NHLs of the nasopharynx show differences between EBV-positive versus EBV-negative cases. The association of EBV-positive cases with expression of CD30 and PD-L1 may be particularly informative for targeted therapies. A significant number of cases expresses SSTR2, which could render them susceptible to somatostatin analogue and peptide receptor radionuclide therapies. Finally, our limited case series suggest that EBV negativity may be associated with a better prognosis.

1. Introduction

Nasopharyngeal lymphoma accounts for approximately 15% of all head and neck lymphomas, with the most common subtypes in the United States being B-cell non-Hodgkin lymphomas (B-NHL), which account for 75% of all cases [1]. Among B-NHLs, diffuse large B-cell lymphoma (DLBCL) is the most common. Relatively little, however, is known about the clinicopathologic features of these rare cases. For example, while Epstein-Barr Virus (EBV) contributes to the pathogenesis of NK/T-cell lymphomas, association of EBV with nasopharyngeal B-NHLs remains unclear. While a few studies examine lymphomas in the sinonasal tracts, which focus primarily on the general features of lymphoma subtypes (both B and T-cell lymphomas), their frequencies, anatomic sites, and related outcomes [2-4], an updated account for the clinicopathologic characterizations of aggressive B-NHLs in this region

is currently lacking, especially in light of their EBV status and expressions of currently tested biomarkers.

Biomarker research in lymphoma has yielded attractive targets for therapeutic interventions. Previous phase I/II clinical trials has shown efficacy of PD-1 blockade in classical Hodgkin lymphoma and refractory/relapsed non-Hodgkin B-cell lymphomas such as DLBCL, primary mediastinal DLBCL, follicular lymphoma, and CLL with Richter transformation [5]. In addition, CD30 overexpression is characteristic of, for instance, anaplastic large cell lymphoma (ALCL) and Hodgkin lymphoma (98% in classical Hodgkin lymphoma), and U.S. FDA approved brentuximab-vedotin in 2011 for treatment of both lymphomas after demonstrated efficacy in clinical trials [6]. Most recently, addition of brentuximab-vedotin to CHOP has shown promising result in CD30-positive peripheral T-cell lymphomas in ECHELON-2 trial [7]. Past studies have shown that EBV-related lymphoproliferative disorders are

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associated with increased PD-L1 and CD30 expression, suggesting the possibility of therapeutic blockade by PD-1 antibody and brentuximab-vedotin [5,8].

Positive somatostatin scintillography of lymphomas had been reported in the 1990s but has not gained attention due to variable expressions and limited sensitivity [9-12]. Of interest, a recent case report documents expressions of somatostatin receptor SSTR2, a G protein-coupled receptor (GPCR) family member, in a DLBCL originally suspected to be a relapsed pulmonary carcinoid tumor due to positive somatostatin scintillography [13]. Another case series also show SSTR2 expressions in various lymphoid malignancies, particularly in DLBCLs and classic Hodgkin lymphomas [14]. In a prior study of 76 germinal center subtype of DLBCL, 28% show strong expression of SSTR2, comparable to that of neuroendocrine tumors, for which somatostatin analogue therapy has been available [15]. Besides DLBCL, other studies have shown SSTR expressions in marginal zone lymphomas and mantle cell lymphomas [16].

In this study, we characterize a two-institutional cohort of aggressive B-NHLs primary to the nasopharyngeal area. In particular, we compare and contrast EBV-positive versus EBV-negative cases and evaluate expression of CD30 and PD-L1, potential markers for targeted therapeutics. Furthermore, we characterize the SSTR2 expression in nasopharyngeal aggressive B-NHLs.

2. Materials and methods

2.1. Case selection

We searched the database from the two institutions for aggressive B-NHLs of the nasopharynx after obtaining appropriate Institutional Review Board approval for the study (NeoGenomics, Aliso Viejo, CA; Yale-New Haven Hospital, New Haven, CT). Cases in which systemic lymphoma was found prior to or concurrently were excluded. We retrieved 53 cases of aggressive B-NHLs, including 48 DLBCLs, two Burkitt lymphomas, two high-grade B-cell lymphomas and one plasmablastic lymphoma. For DLBCL, the Hans criteria was used to determine the germinal center versus non-germinal center type. All diagnosis were made according to current WHO criteria [17] using appropriate ancillary studies. Patient information regarding treatment regimens and clinical follow-up were obtained from the electronic medical record (EMR) at Yale-New Haven Hospital.

2.2. Immunohistochemistry and fluorescence in situ hybridization (FISH)

All immunohistochemical (IHC) studies performed previously for diagnoses were reviewed. For IHC performed at Yale, the following antibodies were applied on formalin-fixed paraffin-embedded (FFPE) tissue sections (see summary of Table 1): CD20 (Dako); CD10 (Cell Margue); Cyclin D1 (Biocare); BCL2 (Dako); BCL6 (Dako); MUM1(Dako); Ki-67 (Dako); cMyc (Abcam); and CD30 (Dako). For selected cases with available tissue blocks (14 in total), PD-L1 (Dako) and

Table 1
Summary of antibodies and reagents.

Antibody	Clone	Vendor	Dilution	Detection method
CD20	L26	Dako	1:200	Ventana
CD10	56C6	Cell Marque	1:40	Refine
Cyclin D1	SP4*	Biocare	1:100	Ventana
BCL2	124	Dako	1:150	Refine
BCL6	PG-B6p	Dako	1:50	Refine
MUM1	MUM1P	Dako	1:50	Ventana
Ki-67	MIB-1	Dako	1:300	Ventana
cMyc	Y69	Abcam	1:100	Refine
CD30	BERH2	Dako	1:300	Ventana
SSTR2	EP149	Epitomics	1:250	Leica's refine polymer
PD-L1	22C3	Dako	–	Dako's FDA pharmDx kit

SSTR2A (Epitomics) IHC were performed at Neogenomics using appropriate controls and protocols. EBV was detected by in situ staining for EBV-encoded small RNAs (EBER). FISH probes for *BCL2*, *BCL6*, and *MYC* were performed on selected FFPE tissue sections.

2.3. Data analysis

The patients were stratified into EBV-positive versus EBV-negative cases and IHC staining patterns and FISH results were compared. PD-L1 staining was evaluated by H-score (intensity score x % cells staining) and interpreted according to standard methods for interpretation of 22C3 using FDA-approved tumor proportion (TPS) scoring. SSTR2 was scored based on the presence or absence of staining (any positive staining was considered positive). The response rate to initial therapy, average interval of disease recurrence, and survival rate at two-year and five-year following the initial diagnosis were used as the primary clinical outcome data.

3. Results

3.1. Clinical features

Most patients were diagnosed at ages > 60 years, with the average age being 65 years (range = 4 to 94). There was slight male predominance (male: female = 1.7:1). All cases derived from the nasopharynx (53%), nasal cavity and paranasal sinuses (45%), and oropharynx (2%). Four of 53 (8%) cases were from immunocompromised patients, including one HIV-positive patient, two patients with post-transplant lymphoproliferative disorders (PTLD), and one patient with concurrent peripheral T-cell lymphoma (PTCL). (Table 2).

3.2. Pathologic features

The 53 aggressive nasopharyngeal B-NHLs included 48 diffuse large B-cell lymphomas (DLBCLs), two Burkitt lymphomas, one double-hit lymphoma, one high-grade B-cell lymphoma, not otherwise specified, and one plasmablastic lymphoma.

The DLBCLs shared defining features including diffuse proliferation of large atypical lymphoid cells with frequent mitotic figures. For tumors with epithelial lining, most tumor cells grew beneath the surface respiratory or squamous epithelium without epitheliotropism. The one case with hard palate involvement showed cortical bone erosion by

Table 2
Clinical features of selected cases.

	Patient characteristics
Average age at diagnosis	65 (4–95)
Male:Female	1.7:1 (33:19)
Locations	
Nasopharynx	27 cases (53%)
Nasal	18 cases (35%)
Sinus	5 cases (10%)
Oropharynx	1 case (2%)
Immune system status	
HIV positive	1 case (2%)
Post-transplant	2 cases (4%)
Concurrent lymphoma	1 case with PTCL (2%)
EBV positive	12 cases (23%)
Immunocompetent	9 cases (17%)
Immunocompromised[a]	3 cases (6%)
EBV negative	41 cases (77%)
Immunocompetent	40 cases (75%)
Immunocompromised[b]	1 case (2%)

EBV: Epstein-Barr Virus; PTCL: Peripheral T-cell lymphoma.
[a] The three immunocompromised patients included one with HIV, one with PTLD, and one with peripheral T-cell lymphoma (PTCL).
[b] The patient had PTLD.

lymphoma cells. Most cases demonstrated intact and uninvolved vasculature in contrast to the common finding of angioinvasion seen in extranodal NK/T-cell lymphomas.

The one double-hit lymphoma case involved the nasopharynx and demonstrated positive *BCL6* and *MYC* translocation. The one case of "high-grade B-cell lymphoma, not otherwise specified" involved the nasal cavity and showed diffuse sheets of intermediate-sized lymphocytes with monotonous round nuclei, open chromatin, and multiple distinct nucleoli and numerous tingible-body macrophages. The morphologic and immunophenotypic features were intermediate between Burkitt lymphoma and DLBCL; FISH studies did not detect any translocations despite MYC (positive in ~85% of cells) and BCL2 (> 50%) overexpression by immunohistochemistry.

The two Burkitt lymphomas consisted of diffuse infiltration of intermediate-sized cells with the classic "starry-sky" appearance and near 100% Ki-67 proliferative indices. One case occurred in a 4-year old boy in the oropharynx and was EBV negative, while the other occurred in a 34-year old man in the nasopharynx with EBV positivity. FISH analysis detected *MYC* gene translocations in both cases.

The one case of plasmablastic lymphoma affected the nasal cavity and demonstrated large cells with plasmablastic differentiation. The tumor cells were negative for B-cell markers such as CD20 but were positive for MUM1 and EBV.

Overall, twelve out of all 53 cases (23%) were EBV positive. No significant differences were found between EBV-positive and EBV-negative cases in terms of age (62 vs 65) and gender distribution. The twelve EBV-positive cases included 10 DLBCLS, one Burkitt lymphoma, and one plasmablastic lymphoma (Table 3). Three of the four immunocompromised patient (one HIV positive patient, one PTCL patient, and one of the two PTLD patients) were EBV positive (Table 2) and had DLBCLs. In comparison, the EBV-negative cohort included 38 DLBCLs, one Burkitt lymphoma, one double-hit lymphoma, and the aforementioned high-grade lymphoma, NOS (Table 3). All patients in the EBV-negative cohort were immunocompetent except one with PTLD (Table 2).

Morphologically, there was significant overlap between EBV-positive and EBV-negative cases. Many of the EBV-positive DLBCLs contained geographic necrosis with abundant mixed reactive lymphocytes, plasma cells, and histiocytes in the background; one case demonstrated prominent histiocytic phagocytosis. Angioinvasion was occasionally seen. The tumor cells in the EBV-positive cases consisted of mostly polymorphous populations of large cells, and many displayed areas of

monomorphous populations of large centroblasts, immunoblasts or Reed-Sternberg-like cells (Fig. 1).

Immunophenotypically, the EBV-positive and EBV-negative cases showed no significant differences in terms of Ki-67 proliferation index (74% vs 84%), or cell-of-origin classification by Hans criteria for DLBCL (60% versus 68% being non-germinal center type, respectively) (Table 3). BCL2 IHC and FISH also did not detect significant differences, although BCL6 IHC and FISH positivity were more frequent in EBV-negative cases in this small cohort. Because MYC expression/translocation has shown some association with worse prognosis in nodal diffuse large B-cell lymphomas, we tried to determine whether a difference existed among EBV-positive versus EBV-negative nasopharyngeal lymphomas. While average expression of MYC by IHC was higher for EBV-negative than EBV-positive cases (45% vs 15%), no significant difference was found in *MYC* translocation by FISH (15% versus 10%, respectively) (Table 3).

3.3. CD30 expression and EBV status

CD30 expression was tested in six EBV-positive and 17 EBV-negative cases. Overall, no association was found between CD30 expression and germinal center versus non-germinal center subtypes. CD30 expression, however, was more frequent in EBV-positive than in EBV-negative cases (4/6 vs 1/17) (Fig. 2 and Table 3); among the six EBV-positive lymphomas tested, four were CD30 positive and two were CD30 negative. Outcome data was only available for one of the four EBV+/CD30+ patients, who died within one year of diagnosis from cardiotoxicity related to chemotherapy.

Among 17 EBV-negative patients, sixteen were CD30 negative (16/17) and only one was CD30 positive(1/17). The one EBV-/CD30+ patient had disease recurrence after 4 years, and the patient died 10 years after the initial diagnosis from unknown cause. On the other hand, two of the 16 EBV-/CD30- patients with available outcome data were alive at 10-year follow-up; one of them had disease recurrence after 11 years and died 14 years after the initial diagnosis; the other one has had no reported disease recurrence. The limited data suggested that, for EBV-negative patients, CD30 positivity potentially carried a slightly worse prognosis than CD30-negative cases. Yet, in comparison with the aforementioned EBV+/CD30+ patient, CD30 positivity in the context of negative EBV still had a much longer survival period. In summary, our small cohort showed that CD30 positivity was correlated with EBV positivity, and EBV and CD30 double positivity might be associated with adverse clinical outcomes.

3.4. PD-L1 expression and EBV status

The association between EBV and PD-L1 expression in Hodgkin lymphomas and aggressive B-cell lymphomas has previously been reported [18-20]. Here, we characterized the expression of PD-L1 in nasopharyngeal lymphomas which had a 23% frequency of EBV infection in our series.

Three of EBV-positive and 11 of EBV-negative cases were tested for PD-L1 expression. Combined, seven of 14 (50%) cases tested demonstrated expressions of PD-L1 within tumor cells. Two of three EBV-positive cases (2/3) and five of eleven EBV-negative (5/11) cases showed positive staining of PD-L1 (Fig. 3). The two EBV-positive DLBCL cases tested showed 3+ staining pattern in at least 40% of tumor cells; on the other hand, the EBV-negative cases demonstrated predominantly 0–2 intensity in no more than 30% of tumor cells. The average H-score was 165 for EBV-positive cases compared with an average of 60 for EBV-negative cases (Table 3).

3.5. SSTR2 expression

In our initial characterization of SSTR2 expressions in aggressive nasopharyngeal B-NHLs, we selected 15 cases for SSTR2 IHC studies

Table 3
Summary of EBV positive and EBV negative cases.

|	EBV + (n = 12)	EBV − (n = 41)
Average age at diagnosis	62 (20–95)	65 (4–94)
Male:Female	7:5 (1.4:1)	24:13 (1.8:1)
Lymphoma types		
DLBCL	10	38
Burkitt	1	1
Double Hit	0	1
Plasmablastic	1	0
NOS	0	1
Germinal-center type	40%	32%
Non-germinal center type	60%	68%
Ki-67	74%	84%
CD30 positivity	67% (4 of 6 cases)	6% (1 of 17 cases)
PD-L1 expression	67% (2 of 3 cases)	45% (5 of 11 cases)
PD-L1 level (average H-score)	165	60
SSTR2	33% (1 of 3 cases)	45% (5 of 11 cases)
MYC IHC (average expression)	15%	45%
MYC FISH	10% (1 of 10 cases)	15% (4 of 27 cases)
BCL2 IHC	64%(7 of 11 cases)	86%(31 of 36 cases)
BCL2 FISH	13%(1 of 8 cases)	10%(2 of 20 cases)
BCL6 IHC	45%(5 of 11 cases)	89%(32 of 36 cases)
BCL6 FISH	0%	28%(5 of 18 cases)
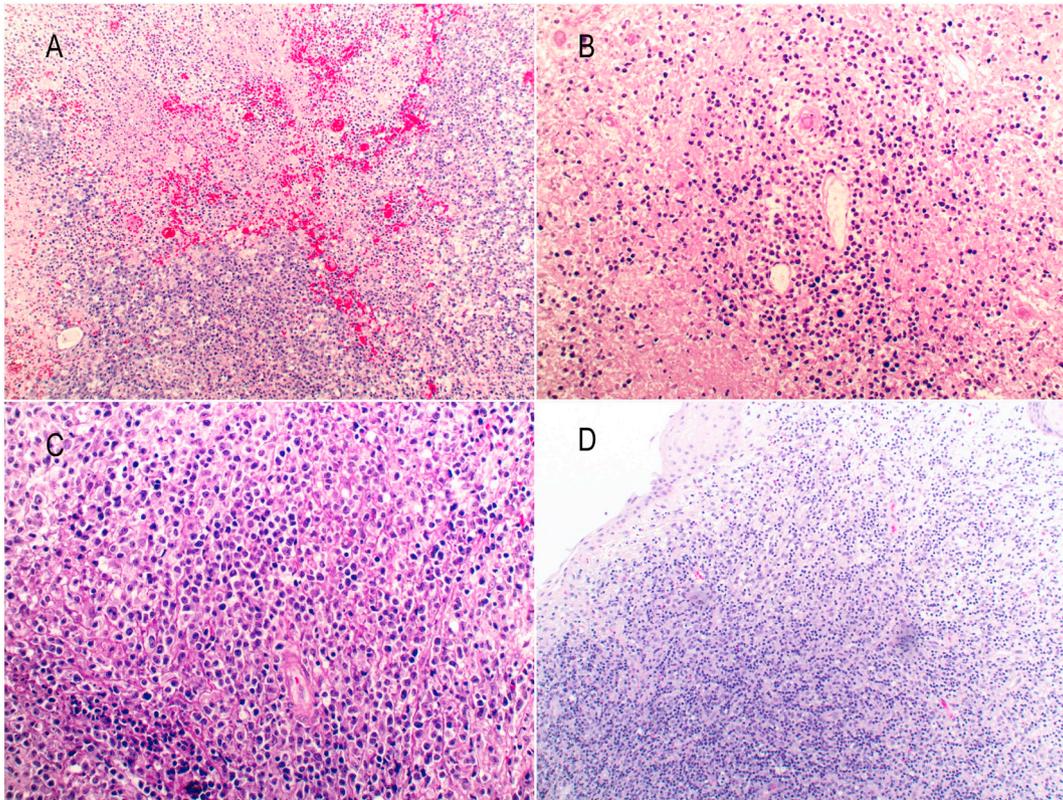
Fig. 1. EBV-positive cases with examples of (A) geographic necrosis, (B) angioinvasion, (C) monomorphous growth of large atypical cells, and (D) abundant mixed reactive lymphocytes, plasma cells, and histiocytes in the background.
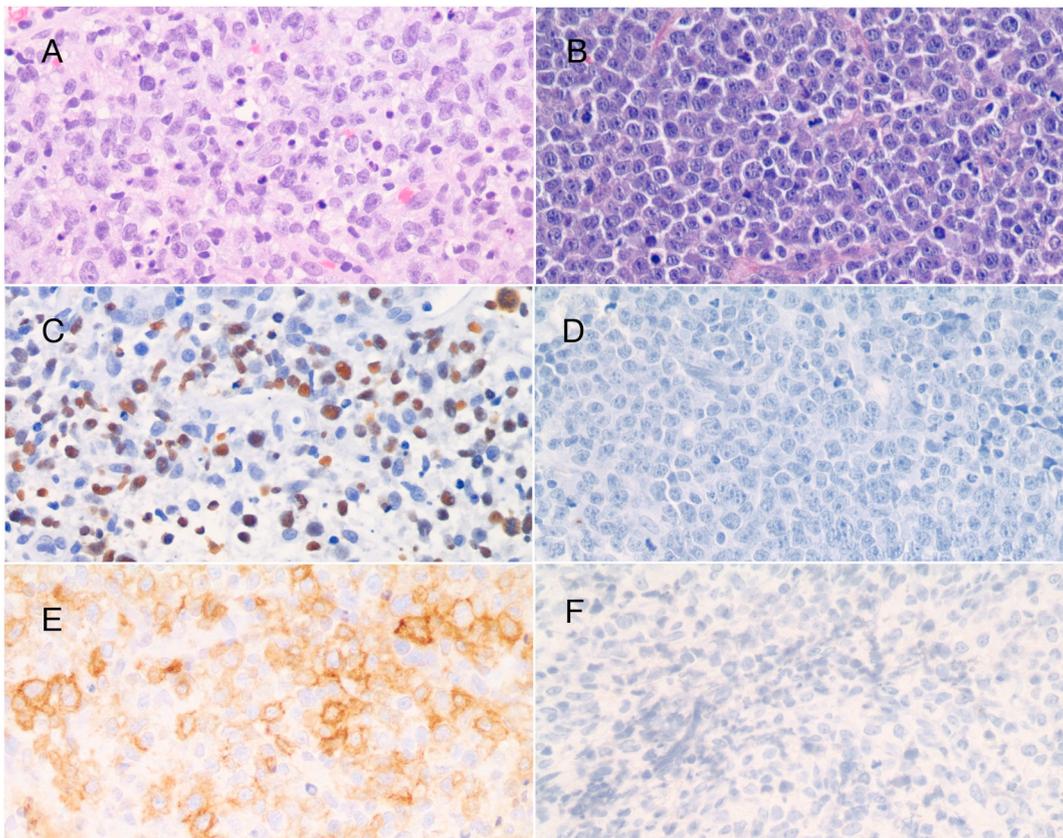

Fig. 2. Representative CD30 expression in EBV-positive cases (A, C, E) and in EBV-negative cases (B, D, F). (A, B) Hematoxylin & eosin; (C, D) EBER FISH; (E, F) CD30.
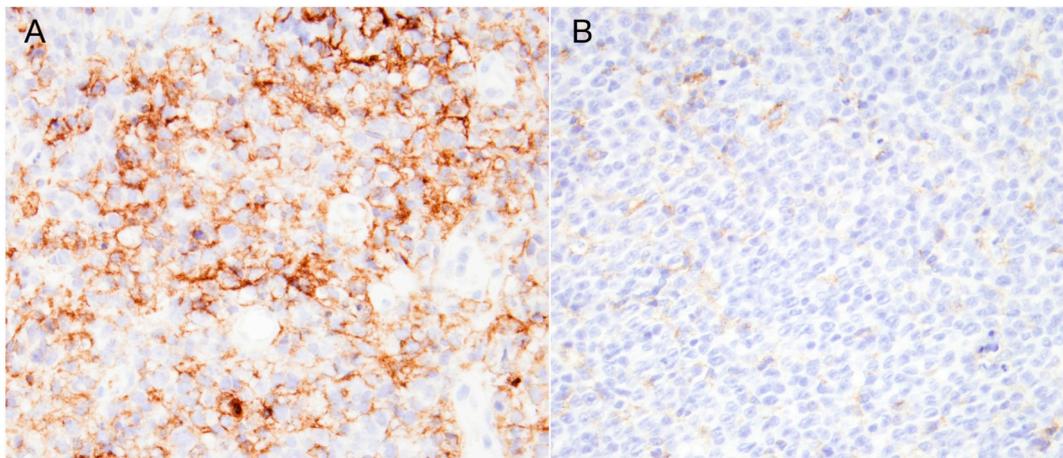
Fig. 3. Representative PD-L1 expression in (A) EBV-positive cases and in (B) EBV-negative cases.

(three EBV positive, 12 EBV negative). In total, six of 15 (40%) cases tested were positive for SSTR2. Three cases affected the nasal cavity and the other three affected the nasopharynx. Stratification by EBV status showed that one of three EBV-positive (33%) cases and five of 11 EBV-negative cases (45%) demonstrated SSTR2 expression. The only EBV+/SSTR2+ DLBCL case involved the nasal cavity and also expressed strong CD30 and PD-L1. The limited sample size, however, precluded correlation analysis between SSTR2 expression and EBV status, PD-L1, or CD30.

We have not identified distinct morphologic differences between SSTR2-positive and SSTR2-negative cases. Five of the six SSTR2-positive cases belonged to the germinal center type and were EBV negative; the sixth SSTR2-positive case was non-germinal center type and EBV positive. In cases that showed clear and strong SSTR2 expression, the staining pattern was predominantly membranous with little to no cytoplasmic staining around the large atypical neoplastic cells (Fig. 4). In cases without SSTR2 expression, faint background staining was observed mostly in macrophages or small vasculatures as documented previously [14].

3.6. Patient outcome and EBV status

Fourteen patients (26%) were available for follow-up, who all received chemotherapy and radiation as first-line therapies. The overall mortality rate was about 50% at 10-year follow-up. We further stratified the patients into EBV-positive versus EBV-negative cases (Table 4). The initial response to chemotherapy, disease free interval, and survival at one, two, and five-year follow-up were obtained from the EMR. The three EBV-positive patients with available outcome data, including one

Table 4
Patient outcome date.

	EBV+ [3]	EBV− [11]
Treatment response, 1st line	1/3 (33%)	8/8 (100%)
Treatment response, 2nd line	–	3/4 (75%)
Disease free interval (average years)	–	6.7 years
Survival, 1 year	0/3	10/10 (100%)
Survival, 2 year	–	8/8 (100%)
Survival, 5 year	–	5/6 (83%)
Survival, 10 year	–	2/3 (67%)

EBV+/CD30+ patient, died within one year of diagnosis; in contrast, the EBV-negative cases showed survival rate of 100% (8/8) and 83% (5/6) at two- and five-year follow-up, respectively. For patients with initial response to therapy and later recurrence (all of them belonged to the EBV-negative cohort), the average recurrence interval was 10 years. While the two EBV-positive patients died from undocumented causes, the third died from cardiopulmonary complications of chemotherapy. For the EBV-negative patients available for follow-up, one likely died from CNS dissemination of lymphoma 13 years after initial diagnosis, one from wound infection unrelated to lymphoma 11 years after diagnosis, and two died from undocumented causes.

4. Discussion

Head and neck region is second only to the gastrointestinal track for extranodal lymphoma involvement; the nasopharynx, as part of the Waldeyer's ring, and the sinonasal tracts are most frequently involved. Among lymphomas that occur primarily in the nasopharynx, extranodal
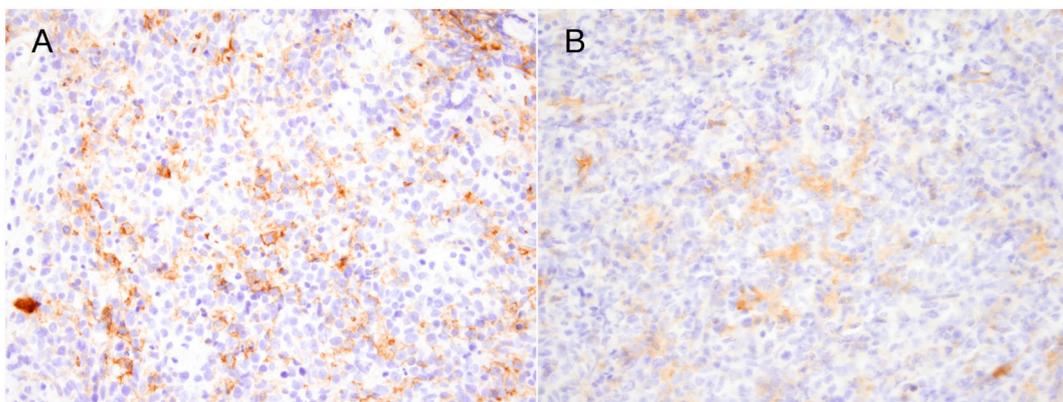

Fig. 4. Representative SSTR2 staining in either EBV-positive (A) or EBV-negative (B) cases.

NK/T-cell lymphoma is most well-characterized. However, primary B-NHL is still the most common, with biological and clinical behavior that is distinct from extranodal NK/T cell lymphomas [1]. Until now, there is a relative lack of clinicopathologic analysis of different subtypes of nasopharyngeal B-NHLs. Here, we present our initial work on a cohort of aggressive large B-cell lymphomas at the nasopharyngeal site, in correlation with some relevant biomarker studies.

A few prior studies have documented some clinocopathologic characteristics of the sinonasal and nasopharyngeal lymphomas. Cuadra-Garcia et al. analyzed 58 cases of sinonasal lymphomas from the Massachusetts General Hospital [2]. Our patient cohort is comparable to Cuardra-Garcia et al. in terms of age range, gender distribution (slight male predominance), and a predominance of DLBCLs as the major histologic subtypes. We notice a rate of 23% EBV positivity in our series, similar to 18% (2/11 cases of DLBCL by EBER) described in Cuardra-Garcia et al.. The percentage is higher than EBV-positive DLBCLs in general, which accounts for < 5–15% of all DLBCL in Asian countries and Latin America, and < 5% in western countries [17]. Cuardra-Garcia et al. mentions a range of EBV positivity among different studies, with one from Japan documenting 40% of sinonasal lymphomas being EBV positive. We, however, have not been able to compare and contrast different ethnicities in our current study.

Most prior studies on sinonasal DLBCLs demonstrate 50–60% 5-year survival after chemoradiation therapy [2,3], yet none has evaluated EBV-positive versus EBV-negative cases. In contrast to these studies, we have specifically focused on the clinicopathologic behaviors of EBV-positive versus EBV-negative cases in aggressive B-NHLs, especially in light of recent research showing that EBV positivity predicts a poor prognosis [21]. In many aspects the EBV-positive large B-cell lymphomas in our series show characteristics similar to that of the WHO subtype EBV-positive DLBCL, NOS. The lymphomas in this study are more likely to be activated B-cell (NGC) type and display frequent CD30 and PD-L1 expressions. The prognosis is also similar to EBV-positive DLBCL, NOS; the three EBV-positive lymphomas with available patient outcome data displayed aggressive behavior, as the patients all died within one year of diagnosis (Table 4). Importantly, EBV-positive DLBCL NOS shows risk stratification by age, with young patients having much better prognosis with long term complete remission > 80% [17]. One of three EBV-positive patients in our series, however, received the diagnosis at age 20 and died shortly after.

Our work further complements prior studies by evaluating immunohistochemical profiles of nasopharyngeal aggressive B-NHLs, particularly new biomarkers of potential therapeutic relevance. CD30 has emerged as an attractive biomarker for various lymphomas. Interestingly, viral infections such as by EBV and HIV have been associated with aberrant CD30 expressions in both T and B cells, though the mechanism has been elusive [6,22]. The EBV + /CD30 + patients in our series carry poor clinical outcomes, in keeping with prior studies based on the CD30 expression status in patients with EBV-positive DLBCL, NOS [23]. Our preliminary data also indicates that, among EBV-negative patients in our series, one patient with CD30 expression had shorter disease-free interval (4 years), in comparison with two other patients with negative CD30 status who showed > 10 years of disease-free interval. However, other studies have suggested CD30-positive DLBCL carries a better prognosis [24]. Future studies on CD30-positive nasopharyngeal lymphomas with patient outcome data will be required to determine whether CD30 expression is an independent predictive marker for patient outcome.

We have also evaluated PD-L1 expression and its association with EBV status in nasopharyngeal aggressive B-cell lymphomas. In latency program II or III, LMP1 expression in EBV-infected cells promotes AP-1 and JAK/STAT pathways to activate the enhancer and promoter elements of CD274 (encoding PDL-1) and accounts for the immune escape mechanisms [18]. In two of three EBV-positive cases with available slides for staining, we find strong PD-L1 expression, which is consistent with the previous findings that 100% of EBV-positive DLBCLs express

PD-L1 (using 5% cell staining) [18]. Our findings that nasopharyngeal EBV-positive DLBCLs frequently express PD-L1 implies that this group of lymphomas will be of interest in future clinical trials in determining clinical response to PD-1 blockade.

Besides CD30 and PD-L1, we have tested SSTR2, a membrane protein of the GPCR family best characterized in neuroendocrine tumors. Several case reports demonstrate SSTR expression in B-cell lymphomas (i.e. DLBCL and MALT) [14,16,25,26]. In our series, one EBV-positive and five EBV-negative cases (total six of 15 cases tested, or 40%) show SSTR2 staining by IHC, corroborating prior case reports documenting scintillographically positive, SSTR2-expressing DLBCLs [14,25]. Also, we have found that SSTR2 expression shows predilection for non-germinal center type DLBCLs (five of six positive cases), which is consistent with earlier findings but whose significance is currently unknown [14,15]. Whether SSTR2 expression is associated with patient outcome remains a future area of research. In addition, the characterization and mechanism of different subtypes of GPCR expressions in different lymphomas will likely be of therapeutic interest, as such knowledge will likely facilitate development of novel targeted drugs.

Overall, our work complements prior studies and advances our understanding of sinonasal lymphomas by specifically evaluating EBV-positive versus EBV-negative aggressive B-cell lymphomas. Available outcome data, though limited, suggest a more aggressive behavior of the EBV-positive than EBV-negative cases. The association of EBV-positive cases with expression of CD30 and PD-L1 may be particularly informative for targeted therapies. This data is in line with previous studies of PD-L1 expression in virus-associated B-cell malignancies. In addition, a significant number of our cases, irrespective of EBV status, expressed SSTR2, which could render them susceptible to somatostatin analogue therapy and peptide receptor radionuclide therapy. Further studies are required to determine the clinical behaviors of SSTR2-expressing lymphomas.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

Acknowledgement

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