

Primary sinonasal DLBCL: High prevalence of MCD subtype and CNS risk

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Dear Editor,

Primary sinonasal diffuse large B-cell lymphoma (SN-DLBCL) is a rare extranodal (EN) lymphoma subtype. A nationwide retrospective cohort study from Denmark reported an incidence of 0.14 per 100,000 person-years, with 5-year overall survival (OS) and progression-free survival (PFS) rates of 56% and 50%, respectively.¹ However, robust nationwide, population-based incidence data for SN-DLBCL outside Denmark remain scarce. In Asian populations, sinonasal lymphomas are more commonly represented by extranodal natural killer/T-cell (EN NK/T-cell) lymphoma, and data specific to SN-DLBCL are limited.² Consequently, the clinical behaviour, molecular characteristics and risk of central nervous system (CNS) involvement in SN-DLBCL are not well-defined, particularly in Asian cohorts. This study reports a single-centre retrospective case series of SN-DLBCL in an Asian population.

In this retrospective study, 8 patients with primary SN-DLBCL were identified, all of whom were pathologically confirmed by biopsy. The baseline characteristics, treatment regimen and outcome of these patients are summarised in Table 1.

The median age at diagnosis was 61.5 years (range, 56–74), and 5 patients were male. The clinical presentation was characterised by a high prevalence of nasal obstruction (62.5%), periorbital swelling with pain (50%) and diplopia (50%), collectively highlighting the locally aggressive nature of SN-DLBCL. In this cohort of 8 patients, next-generation sequencing (NGS) was performed in 7 patients, except 1 patient pathologically diagnosed at an outside hospital before referral. Genetic analysis demonstrated that all 7 patients were classified as the *MYD88/CD79B*-mutated (MCD) (85.7%, 6/7)/MCD-like (14.3%, 1/7) subtype DLBCL. In this study, MCD referred to cases with co-occurring *MYD88* and *CD79B* mutations, whereas MCD-like referred to cases harboring *MYD88* mutation without *CD79B* mutation. The most common additional mutations were in *PIM1* (71.4%, 5/7) and *KMT2D* (42.9%, 3/7). Alterations in *KMT2C*, *EP300*,

NOTCH1 and *MPEG1* were each found in 28.6% of the cohort (2/7). This predominant molecular feature is consistent with previous studies³ and bears a strong resemblance to the profile of primary CNS DLBCL. CNS involvement is an uncommon complication, occurring in approximately 2–10% of patients with DLBCL, and carries a very poor prognosis.⁴ The CNS-International Prognostic Index (CNS-IPI) is the most commonly used tool for estimating risk of CNS recurrence, and CNS prophylaxis is recommended for high-risk patients.⁵ In the rituximab era, several additional high-risk features not captured by the CNS-IPI have been recognised, including dual expression of myelocytomatosis oncogene/B-cell lymphoma 2; the activated B-cell-like molecular subtype; certain EN sites involvement (testicular, uterine, breast); and intravascular large B-cell lymphoma.⁶ Furthermore, involvement of anatomical sites in the head and neck region (e.g. paranasal sinuses, hard palate) and areas close to the CNS (epidural space, dura, paravertebral region and orbit) has also been reported to confer an increased risk.⁷ A few studies have reported the association between SN-DLBCL and an increased risk of CNS involvement. Murawski et al.⁸ analysed 11 consecutive trials from the German High-Grade Non-Hodgkin Lymphoma Study Group. Ninety-three SN-DLBCL patients were identified out of 4155 patients (2.24%), and further analysis revealed that only paranasal sinus involvement was associated with a relative high risk of CNS relapse (2-year incidence 6.4%). Eriksen et al. analysed 116 SN-DLBCL patients registered in the Danish National Pathology Registry between 1980 and 2018. Among these patients, 30 of 116 (25.9%) developed recurrence and localised spread/progression, with 9 had CNS involvement.⁹ In this cohort, 2 of 8 patients (25%) presented with CNS involvement at diagnosis and 1 patient suffered from first CNS disease after complete remission (CR). At diagnosis, Cases 2 and 3 presented with CNS involvement, and successfully achieved CR induced by rituximab-cyclophosphamide, doxorubicin

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Table 1. Baseline characteristics, therapeutic regimen and outcome of primary SN-DLBCL patients.

No.	Sex	Age	IHC/FISH	NGS (tier I variants, genes)	Symptoms	Site of involvement at diagnosis	AA stage	Treatment regimen	Best response	CNS relapse	Status at last follow-up
1	M	74	Non-GCB	U/K	Nasal symptoms: nasal obstruction, rhinorrhoea Eye symptoms: periorbital swelling, periorbital pain, epiphora, diplopia Facial symptoms: facial swelling, facial pain	Nasal cavity, paranasal sinuses	IVA	R-CHOP R-HD-MTX	CR	Yes	PFS: 9.83 months OS: 17.00 months Outcome: died of CNS relapse
2	F	62	Non-GCB Triple expression EBER (-) No MYC rearrangements	MYD88 CD79B KMT2D B2M CREBBP TP53	Facial symptoms: facial swelling, facial pain	Paranasal sinuses, lymph node, CNS	IVA	R-MTX-CHOP	CR	Yes	PFS: 20.37 months OS: 20.37 months Outcome: died of CNS relapse
3	F	59	GCB Triple expression EBER (-) No MYC rearrangements	MYD88 CD79B PIM1 KMT2C BTG1 IRF8	Eye symptoms: diplopia, blurred vision, limited eye movement	Paranasal sinuses, lymph node, bone marrow, CNS	IVB	R-MTX-DA- EPOCH plus Orelabrutinib	CR	No	PFS: 25.80 months OS: 25.80 months Outcome: alive with CR
4	M	61	GCB EBER (-) No MYC rearrangements	MYD88 CD79B PIM1 KMT2D EP300 BTG2 DTX1	Nasal symptoms: nasal obstruction, rhinorrhoea, epistaxis	Nasal cavity, paranasal sinuses, bone marrow	IVB	Pola-R-CHP R-HD-MTX Auto-HSCT Orelabrutinib	CR	No	PFS: 19.07 months OS: 19.07 months Outcome: alive with CR
5	M	56	Non-GCB EBER (-) No MYC rearrangements	MYD88 CD79B PIM1 KMT2C MPEG1 NOTCH1 PRDM1	Eye symptoms: periorbital swelling, periorbital pain, limited eye movement	Paranasal sinuses	IA	R-DA-EPOCH R-HD-MTX Orelabrutinib	CR	No	PFS: 20.87 months OS: 20.87 months Outcome: alive with CR

Table 1. Baseline characteristics, therapeutic regimen and outcome of primary SN-DLBCL patients. (Cont'd)

No.	Sex	Age	IHC/FISH	NGS (tier I variants, genes)	Symptoms	Site of involvement at diagnosis	AA stage	Treatment regimen	Best Response	CNS relapse	Status at last follow-up
6	F	66	Non-GCB Double expression EBER (-) MYC-IGH rearrangements	MYD88 CD79B NOTCH1 CIITA	Nasal symptoms: nasal obstruction, hyposmia	Nasal cavity	IA	R-DA-EPOCH R-HD-MTX	CR	No	PFS: 10.37 months OS: 10.37 months Outcome: alive with CR
7	M	61	GCB Triple expression EBER (-) No MYC rearrangements	MYD88 PIM1 CCND3 SGK1	Nasal symptoms: nasal obstruction, rhinorrhoea, hyposmia Eye symptoms: periocular swelling, periocular pain	Nasal cavity, paranasal sinuses	IB	Pola-R-CHP R-HD-MTX	PR	No	PFS: 6.63 months OS: 6.63 months Outcome: alive with PR
8	M	66	GCB Triple expression EBER (-) No MYC rearrangements	MYD88 CD79B PIM1 KMT2D EP300 MPEG1 TRAF3	Nasal symptoms: nasal obstruction, epistaxis Eye symptoms: periocular pain, periocular swelling, diplopia	Nasal cavity, paranasal sinuses	IB	Pola-R-CHP	U/K	No	PFS: 4.33 months OS: 4.33 months Outcome: alive with disease

AA stage: Ann Arbor stage; auto-HSCT: autologous hematopoietic stem cell transplantation; CHOP: cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone; CNS: central nervous system; CR: complete remission; EBER: Epstein-Barr virus-encoded ribonucleic acid; F: female; FISH: fluorescence in situ hybridisation; GCB: germinal centre B-cell; IGH: immunoglobulin; IHC: immunohistochemistry; LN: lymph node; M: male; MTX: methotrexate; MYC: myelocytomatosis oncogene; NGS: next-generation sequencing; OS: overall survival; PFS: progression-free survival; PR: partial remission; Pola-R-CHP: polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone; R: rituximab; R-DA-EPOCH: dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and rituximab; R-HD-MTX: rituximab and high-dose methotrexate; U/K: unknown

hydrochloride, vincristine sulphate and prednisolone-like immunochemotherapy combined with high-dose methotrexate (HD-MTX). Case 2 declined subsequent consolidation therapy with autologous hematopoietic stem cell transplantation (auto-HSCT) and maintenance therapy with Bruton's tyrosine kinase (BTK) inhibitors, experienced isolated CNS relapse 6.4 months after completion of induction chemotherapy, and died 7 months after relapse. In contrast, Case 3 received BTK inhibitor therapy throughout the induction, consolidation and maintenance phases, which may have contributed to sustained remission and prolonged survival. Of the remaining 6 patients without CNS involvement at diagnosis, all have either completed or are currently scheduled to receive 2 cycles of HD-MTX as CNS prophylaxis. Long-term outcomes differed by treatment. Case 1 managed without auto-HSCT consolidation or BTK inhibitor maintenance, achieved initial CR but developed an isolated fatal CNS relapse 15.77 months after completion of induction chemotherapy. In contrast, Cases 4 and 5, who received auto-HSCT and/or BTK inhibitor therapy, have maintained sustained CR. With a median follow-up of 19.07 months (range, 4.33–25.80) for the entire cohort, the median CNS involvement-free survival was 20.37 months (95% confidence interval 0.00–49.75). Neither median PFS nor OS had been reached (Supplementary Fig. S1).

Findings show that SN-DLBCL patients predominantly exhibited an MCD/MCD-like molecular subtype and demonstrated a high frequency of CNS involvement. This propensity may be attributed to both the anatomical proximity of the sinonasal region to the CNS and the intrinsically aggressive molecular features. Therefore, the NGS testing appears essential for risk stratification. In resource-limited settings, a cost-effective alternative, such as digital polymerase chain reaction to detect key mutations (e.g. *MYD88* and *CD79B*), should be considered to identify patients with the MCD molecular profile. These clinical observations further suggest that a prophylactic strategy consisting only 2 cycles of HD-MTX may be insufficient for patients with the MCD/MCD-like subtype of SN-DLBCL. Therefore, the authors recommend that CNS prophylaxis with HD-MTX be combined with auto-HSCT consolidation and/or BTK inhibitors maintenance, which has shown promising CNS penetrance and efficacy in genetically MCD subtype. However, these observations are tempered by limitations, including the single-centre, retrospective design, small sample size, limited follow-up duration and variations in treatment regimens, which may affect statistical power, the assessment of long-term relapse risk, and the generalisability of the findings, under-

scoring the need for further studies to validate these results and develop evidence-based management strategies.

Supplementary material

Fig. S1. Kaplan–Meier curves of the 8 primary SN-DLBCL patients for CNS involvement-free survival, progression-free survival and overall survival.

Ethics statement

This study was approved by the Institutional Ethics Committee of Xuanwu Hospital, Capital Medical University, Beijing, China (2025-010-002).

Declaration

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