Recapitulating classic Hodgkin’s: primary mediastinal B cell lymphoma

Abstract

The world health organization (WHO) designates the primary mediastinal B cell lymphoma as a unique entity with distinct clinical, morphological and biological attributes which comprises of an estimated 2%-4% of the non Hodgkin’s lymphoma. The median age of emergence is at 35 years and a female to male ratio of (F:M) 1.7-2.0:1 is elucidated. The lymphoma appears as a bulky mediastinal mass situated in the anterior or upper mediastinum with invasion of abutting anatomical thoracic structures such as the chest wall, pleura, lungs, pericardium and heart besides a pleural or pericardial effusion in an estimated 30%-50% instances. The lymphoma simulates the histology of a nodular sclerosis Hodgkin’s lymphoma (NSHL) and depicts a post germinal centre phenotype (CD10-, BCL6+/-, MUM1+). Gene expression profiling (GEP) depicts a reoccurring amplification of JAK2 situated on chromosome band 9p24.1 in approximately 50%-70% instances. The lymphoma exhibits a deterioration of the NFKB and JAK/STAT signalling networks which inhibits apoptosis, besides a specific copy number chromosomal gains of REL and JAK2 oncogene with a decline of tumour necrosis factor alpha induced protein 3 (TNF AIP3) or the A20 gene. JAK/STAT signalling cascade is activated chiefly by interleukin 4 and 13 and augments tumour proliferation. Elevated serum lactate dehydrogenase (LDH) is a singular laboratory abnormality 70%-80% instances. Prognostic factors cogitating a declining survival comprise of age greater than 40 years, clinical stage III and IV, bulky disease, male sex, poor performance status (PS) and serum lactate dehydrogenase (LDH) greater than twice the upper normal limit (> 2 UNL). Therapeutic regimen administered in PMBCL is a combination of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R CHOP). Dose adjusted etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin with rituximab (DA EPOCH R) can efficaciously treat the de novo lymphoma.

Preface

An exceptional subcategory of non Hodgkin’s lymphoma preponderant in adolescents and young adults (AYAs) is constituted by the primary mediastinal B cell lymphoma (PMBCL). The lymphoma (PMBCL) was initially categorized as a subtype of diffuse large B cell lymphoma (DLBCL). The contemporary classification of the world health organization (WHO) designates the primary mediastinal B cell lymphoma as a unique entity with distinct clinical, morphological and biological aspects. Primary mediastinal B cell lymphoma (PMBCL) enunciates an annual incidence of 0.4 /million population. The lymphoma (PMBCL) comprises of an estimated 2%-4% of the non Hodgkin’s lymphoma and approximately 6% of diffuse lymphomas (DLBCL). Caucasians and young adults are implicated and the disorder displays a median age of emergence at 35 years, a female prevalence and a female to male ratio of (F:M) 1.7-2.0:1. Familial PMBCL concurs with 5533C>A mutation of the MLL gene. Primary mediastinal B cell lymphoma is considered as a radiotherapy sensitive lymphoma.

Clinical elucidation

Primary mediastinal B cell lymphoma (PMBCL) classically appears as a bulky mediastinal mass with a localized infiltration of tumour cells. An enlarged, rapidly evolving tumour aggregate situated in the anterior or upper mediastinum is cogitated. The neoplasm invades abutting anatomical structures of the thorax such as the chest wall, pleura, lungs, pericardium and heart. A pleural or pericardial effusion ensues in an estimated 30%-50% instances. Majority (80%) of the subjects elucidate a clinical stage I or II locally advanced disease. Around 75% individuals demonstrate a bulky disease with the tumour magnitude exceeding 10 centimetres. Lymph node incrimination is exceptional in the non-mediastinal sites. Bone marrow is infiltrated in specific instances. The lymphoma reoccurs to disseminate to extra nodal organs such as kidney, adrenal, liver, central nervous system and infrequently to distant lymph nodes. Typical constitutional symptoms include cough, dyspnoea, tachyapnoea, venous thrombosis, chest pain or dysphagia, usually less than three month duration and is engendered by tumour invasion or compression. An estimated half (50%) of the subjects delineate a “superior vena cava syndrome” with ineffecult respiratory tract function and movement, compression of the major blood vessels and a consequent emergence of the syndrome. Systemic symptoms such as weight loss and fever are exceptional and elucidated in approximately one fifth (<20%) instances.

Histological enunciation

The histology of primary mediastinal B cell lymphoma simulates that of a nodular sclerosis Hodgkin’s lymphoma (NSHL). The lymphoma (PMBCL) is engendered from thymus / thymic B cells with an activated germinal centre or post germinal centre phenotype. An activation induced cytidine (AID) gene is consistently elucidated. The enlarged or medium sized, heterogeneous tumour cells demonstrate an abundant, pale-staining cytoplasm with heterogeneous oval, irregular or pleomorphic nuclei akin to those encountered in the Reed Sternberg cells or the nuclei can be multi-lobated as in diffuse lymphoma (DLBCL). Characteristic sclerosis segregates the tumour tissue into diverse aggregates. However, the demarcating collagen is constituted of fine bands, unlike the broad, coarse collagen of nodular sclerosis Hodgkin’s lymphoma (NSHL).
Immune-phenotype

Tumour cells are devoid of cytoplasmic or surface immunoglobulin. The cells elucidate B cell related antigens such as CD19+, CD20+, CD22+, CD79a+ and CD45+. B cell transcription factors such as PAX5+, OCT2+ and BOB1+ are frequently exemplified. A singular component of B cell receptor is enunciated as CD79a. Majority (80%) of instances are immune reactive to CD30+ though the reaction is faint with reduced homogeneity, contrary to the reaction demonstrated with classic Hodgkin’s lymphoma (c HL) and anaplastic large cell lymphoma (ALCL). An immune reactive CD30+ is advantageous in deciding therapeutic protocols applicable to Hodgkin’s disease and anaplastic large cell lymphoma (ALCL). Malignant lymphoid cells are reactive to BCL2+ (55%-80%), CD23+(70%), a variable reaction to BCL6+ (45%-100%) and a lack of reactivity to CD10-(8%-32%) and CD15-(3). MAL gene appears in a specific population of B lymphocytes, the thymic medullary cells. MAL is situated on the long arm of chromosome 2, encodes a protein and is enunciated in an estimated 70% subjects. Diffuse large B cell lymphoma (DLBCL) and classic Hodgkin’s lymphoma (c HL) delineate the MAL gene exceptionnally. Thus, MAL gene can demarcate PMBCL from diffuse lymphoma (DLBCL) which depicts the genetic rearrangement in roughly 3% instances. The histo-compatibility antigens (HLA) class I and II are down regulated or absent in PMBCL. Multiple myeloma 1/Interferon regulatory factor 4 (MUM1/IRF4 ) are demonstrated in approximately half (45%) of the instances and depict an inferior outcome. Classification of majority (97%-98%) of primary mediastinal B cell lymphoma (PMBCL) and classic Hodgkin’s lymphoma (c HL) is achieved with three immune markers such as CD79a, BOB1 and Cyclin E. The discernment of immune phenotype is crucial for appropriately differentiating the lymphoma (PMBCL) (Figure 1-13).
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Figure 7 PMBCL fine collagen bands with compartmentalization of the lymphoid neoplasm.

Figure 8 PMBCL cellular and nuclear irregularity with hyperchromasia.

Figure 9 PMBCL marked variation in cellular and nuclear features of the tumour cells with prominent nucleoli.

Figure 10 PMBCL collagen with disseminated and clustered lymphoid tumour cells.

Figure 11 PMBCL nuclear hyperplasia, hyperchromasia, anisonucleosis and anisocytosis of lymphoid cells.

Figure 12 PMBCL immune reactive CD20+.

Figure 13 PMBCL immune reactive BCL2+.

Molecular characteristics

Gene expression profiling (GEP) transcriptional signature of the lymphoma (PMBCL) recapitulates that of classic Hodgkin’s lymphoma (c HL). Recurring amplification of JAK2 situated on chromosome band 9p24.1 is elucidated in approximately 50%-70% instances. Chromosomal translocation of C II TA is exemplified in roughly 40% subjects. Thymus propagates tumour cells on account of enhanced expression of programmed death ligands 1 and 2 (PDL-1 and PDL-2) with a reduced modulation of major histocompatibility complex (MHC) class II molecules. Chromosomal gains of 2p16 initiates the replication of REL proto-oncogene thereby encoding a transcription factor of the NFkB family. Somatic hyper-mutation of immunoglobulin (Ig) genes and BCL6 detected in PMBCL ascertains a post germinal centre phenotype (CD10-, BCL6+/−).
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MUM1 (+) demonstrated by the malignant cells. The genetic expression of BCL6 is dissimilar in diffuse lymphoma (DLBCL) and follicular lymphoma (FL). Gene expression profiling (GEP) demonstrates genetic up-regulation in one third (34%) of PMBCL, concurrent with Hodgkin’s lymphoma. The genetic over expression is concomitant to the NFκB and JAK/STAT signalling pathways. Malignant phenotype of primary mediastinal B cell lymphoma exhibits a deterioration of the NFκB and JAK/STAT signalling networks which inhibits apoptosis. The NFκB network is a critical transcription factor for the proliferation, survival and constitutive action of NFκB domain. Alternative up-regulation of TNF receptor super-family is initiated, thereby activating the signalling pathway with enhancement of NFκB complex. A20 protein functions as a negative regulator of IKK and NFκB. Genes such as TNAIP3 encode this protein and are mutated in roughly one third (36%) instances with concomitant constitutive activation of NFκB. A nuclear NFκB complex protein such as REL activates the NFκB pathway. Genomic gains and amplification of the REL proto-oncogene, the locus of which is situated on the short arm of the chromosome 2p, is discerned in greater than half (>50%) instances of PMBCL in concordance with the nuclear localization of REL. Primary mediastinal B cell lymphoma also depicts specific copy number chromosomal gains of REL and JAK2 oncogene with a decline of tumour necrosis factor alpha induced protein 3 (TNF AIP3) of the A20 gene. The JAK/STAT mechanism provides an adjunctive and major pathway for the proliferation of tumour cells. The JAK / STAT signalling cascade is activated by the interleukin (IL) receptors chiefly interleukin 4 and 13 (IL 4 and 13). Anomalies are discerned within the pathway, manifested with elevated interleukin 13(IL13) receptor. Genomic amplification of chromosomal regions 9-9p24.1, which constitutes the locus of JAK2, is discovered in two thirds (63%) instances of PMBCL. Elevated levels of JAK2 m RNA and protein co-exist, thus activating the JAK/ STAT cascade with consequent cellular proliferation. Chromosomal amplification of 9p24.1 and up-regulation of JAK2 is accompanied by enhanced immune regulatory programmed death (PD-1) ligand with consequent depletion of T lymphocytes. Constitutive activation of STAT6, the principal protein of JAK/STAT pathway, is characteristic of the lymphoma (PMBCL). Somatic mutation of STAT6 DNA binding domain is elucidated in an estimated one third (36%) instances of PMBCL, thereby defining the dys-regulated JAK/STAT network in the pathogenesis of PMBCL. Genetic encoding of suppressor of cytokine signalling 1 (SOCS-1), a negative regulator of the pathway, is mutated in PMBCL and mediatinal cell clusters. Consequently, a delayed degradation and extensive phosphorylation of JAK2 proteins is manifested. PTNP1, an associated negative regulator of the JAK/STAT pathway, is mutated in approximately 22% of PMBCL with consequent amplified phosphorylation of JAK2 and a worsening progression free survival (PFS). Decimating cytotoxic CD8+ T lymphocyte quantification concurs with a poor prognosis. Gene expression profiling (GEP) or immune-histochemical evaluation demonstrates a declining major histo-compatibility antigen ( MHC) class I and II genes and proteins in PMBCL. Elucidation of major histo-compatibility antigens ( MHC) is controlled by the trans-activator of MHC class II molecule CITA. Genomic discontinuity of CITA molecule is detected in one third (38%) instances of PMBCL. A reduction of MHC class II molecules concurs with a declining survival. Genetic modifications of CITA influences the programmed cell death ligand 1 (PD-L1) situated on tumour cell surface and immune reactivity for PD-L2 with CD273 and PD-L1 with CD274 is cogitated. The immune markers correlate with co-stimulatory signal transduction betwixt the tumour cells and PD-1 receptors situated on T lymphocytes, which along with T cell receptor signalling regulates the function of T lymphocytes. Enhancement of PDL-1 and PDL-2 depletes infiltrating T lymphocytes and thus immune surveillance of malignant cells is averted. Genes encoding PDL-1 and PDL-2 are confined to 9p24.1 locus, identical to the JAK2 mechanism. Genetic modifications of PDL-1 locus is determined in roughly one fifth (20%) subjects of PMBCL and include break apart amplifications and/or chromosomal gains. Genomic rearrangements are accompanied by excessive PDL-1 protein. Programmed cell death ligand 1 (PD-L1) is elevated in PMBCL with an adjudicative modulation of PD-L1. Enhanced PD-L1 appears on an estimated 71% of the malignant lymphoid cells(PMBCL) and tumour associated macrophages, appropriately discerned with immune histochemistry. Partial prohibition of JAK2 protein molecules with drug conjugates such as Fedatinib decreases the phosphorylation of JAK2 and associated proteins of STAT signalling pathway in classic Hodgkin’s lymphoma(c HL) and primary mediastinal B cell lymphoma ( PMBCL). Enunciation of PD-L1 may thus be decimated by the agent.

Concordant diagnosis

Primary mediastinal B cell lymphoma mandates a distinction from adjunctive lymphoid malignancies, particularly within the mediastinal location:

a. Gray zone lymphoma or an unclassifiable B cell lymphoma with morphological aspects betwixt the diffuse lymphoma (DLBCL) and a classic Hodgkin’s lymphoma(c HL).

b. Composite lymphoma comprising of dual subtypes of primary mediastinal B cell lymphoma (PMBCL) and a classic Hodgkin’s lymphoma (c HL).

c. Sequential mediastinal lymphoma with a preceding primary mediastinal B cell lymphoma (PMBCL) reoccurring as a Hodgkin’s lymphoma (HL).

d. Diffuse lymphoma (DLBCL) with an anterior mediastinal tumefaction.

e. Nodular sclerosis category of classic Hodgkin’s lymphoma.

f. T cell lymphoblastic lymphoma.

g. Thymoma.

h. Germ cell tumours.

i. Metastatic carcinomas.

Investigative assay

Primary mediastinal B cell lymphoma (PMBCL) is characteristically restricted to the mediastinum. Lymphoid malignancy devoid of incriminated peripheral lymph nodes necessitates invasive and additional diagnostic procedures. Mediastinoscopy, anterior mediastinoscopy or a percutaneous guided core needle biopsy with a computerized tomography (CT) guidance is a prerequisite. Abundant and/or adequate collection of surgical tissue is recommended on account of cellular decimation during tissue extraction. Characteristic clinical enunciation and histological assessment with concordant immune histochemical assay acceptably classifies the neoplasm. Diagnostic procedures indicated for evaluating the clinical stage of lymphoma incorporate an extensive clinical history, a comprehensive general physical examination, a whole body computerized tomography (CT) scan, a bone marrow biopsy, a complete blood count and serum biochemistries. An elevated
serum lactate dehydrogenase (LDH) is detected in an estimated 70%-80% instances as a singular laboratory abnormality. Serum β2 micro-globulin generally displays normal values. As PMBCL is a fluoro deoxy glucose (FDG) avid lymphoma, a positron emission computerized tomography (PET CT) scan can be included at initial diagnosis and at end of treatment (EOT). Clinical stage is assessed with the classic Ann Arbor staging and majority (75%) of instances of PMBCL exhibit a clinical stage I or II disease.\textsuperscript{13,14}

**Prognostic outcomes**

The lymphoma depicts a 5 year survival of 85%. Diverse ethnicities especially Asians, Hispanic, American Indian and Alaskan Natives demonstrate a reduced survival (70%).\textsuperscript{2} The prognostic decline is 3.5 times greater with elderly beyond 60 years of age and with clinical stage III/IV (80% mortality), in contrast to a cohort of 18-30 years and stage I/II disease. The lymphoma (PMBCL) has recently been detected across various ethnic categories and specifications (age, gender, race) as mentioned.\textsuperscript{2,3} Tumour risk assessment and stratification necessitates the application of an international prognostic index (IPI). Benefits of an IPI are minimal as factors of risk assessment such as age greater than 60 years and clinical stage III or IV may not be pertinent. Thus, assessment of disease stage may lack uniformity or concurrence with aforementioned parameters. A mediastinal tumour invading in continuity and disseminating into the anatomical thoracic structures is categorized as stage IIE or stage IV. Extensive tumour dispersal within extra-nodal organs such as liver, spleen, bone marrow or central nervous system is designated as clinical stage IV. Tumour infiltration within abutting thoracic viscera such as pleura, pericardium, thoracic wall and lungs denominates clinical stage II E.\textsuperscript{1,6} Prognostic factors delineated with declining survival comprise of age greater than 40 years, a clinical stage III and IV, bulky disease, male sex, poor performance status (PS) and serum lactate dehydrogenase (LDH) greater than twice the upper normal limit (>2 UNL).\textsuperscript{5,5} The international prognostic index (IPI) is critical for estimating survival, particularly with the institution of R CHOP. Emergence of pleural and/or pericardial effusion is an adverse attribute. “Low risk” group with an absence of probable factors (risk factors=nl) depicts a favourable 4 year overall survival (OS) of 97% and a progression free survival (PFS) of 89%. Concurrence of two detrimental factors categorizes the subject as “high risk” with an inferior overall survival (OS) of 72% and a progression free survival (PFS) of 44%.\textsuperscript{3,6}

**Therapeutic options**

Novel therapeutic antibody conjugate employed for treating PMBCL targets the JAK/STAT signalling pathway in addition to PD-1/PDL-1. Contemporary trials for evaluating drug conjugates such as Nivolumab, a fully humanized immunoglobulin G4 monoclonal antibody specific for the programmed death ligand PD-1, is adopted in relapsed or refractory lymphoma (PMBCL or DLBCL) ineligible for transplant.\textsuperscript{14,15} Therapeutic regimen administered in PMBCL is a combination of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R CHOP), although it is ineffective in specific instances. Consolidative mediastinal radiotherapy can be adopted as an adjunctive modality. Mediastinal radiotherapy incurs a significant delayed toxicity with an antecedent mortality, cardiovascular complications and the emergence of secondary tumours.\textsuperscript{13,15} Thus, a reduced radio-therapeutic dosage is necessitated with mediastinal lymphomas. Subjects with a clear end of treatment 18 fluorodeoxy glucose positron emission tomography (EOT FDG PET) scan can obtain sustained disease remissions and are devoid of extended therapy. Additionally, positive predictive value (PPV) of an end of treatment positron emission tomography (EOT FDG PET) scan following a dose adjusted etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin with rituximab (DA EPOCH R) therapeutic regimen remains debatable.\textsuperscript{3} Dose adjusted etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin with rituximab (DA EPOCH R) can treat the de novo lymphoma (PMBCL) with an 8 year event free survival (EFS) of 90.6% and an overall survival (OS) of 94.7%. Singular R CHOP is inadequate in numerous instances of PMBCL. Primary induction failure appears in an estimated 21% and requires a post therapeutic combination radiotherapy.\textsuperscript{4} R CHOP versus a DA EPOCH R as an initiating therapy for PMBCL delineates an identical 2 year progression free survival (PFS) or an overall survival (OS) although radiotherapy is frequently associated with R CHOP (59% versus 13%). Concurrence of therapeutic modalities produces superior outcomes. Subjects with an unacceptable end of treatment 18 fluorodeoxy glucose positron emission tomography (EOT FDG PET) scan following therapy with R CHOP mandate a consolidation radiotherapy. However, post treatment radiotherapy is infrequent with the DA EPOCH R regimen, regardless of the status of EOT FDG PET. Thus, individuals with a favourable EOT FDG PET demonstrate minimal disease recurrence and an addendum of mediastinal radiotherapy is not advantageous.\textsuperscript{13,15} Serial scans of fluorodeoxy glucose positron emission tomography (FDG PET) imaging is efficacious in demarcating a disease persistence from post therapeutic inflammatory transformation.\textsuperscript{3,6} Serial imaging in concordance with an inadequate EOT FDG PET demonstrates a comprehensive reduction in the maximum standard uptake values (SUV max) of the tumour. Therapeutic inadequacy as detected with serial FDG PET exhibits an elevation of the SUV max irrespective of the configuration of EOT FDG PET. PMBCL, when treated with the DA EPOCH R regimen enunciates a 3 year event free survival (EFS) of 85.9% and an overall survival (OS) of 95.4%. An estimated 14.9% individuals are administered post treatment radiotherapy. Subjects managed with a DA EPOCH R depict a suitable EOT FDG PET in an estimated three fourths (75%) and roughly 95.4% individuals appear progression free. As the morphology of PMBCL induces substantial false positive EOT FDG PET scans, appropriately modified clinical conclusions are mandated in individuals on DA POCH R. A singular assay of EOT FDG PET may not precisely outline therapeutic failure, although serial FDG PET imaging can differentiate residual disease from post therapeutic inflammatory aberrations.\textsuperscript{3,6} Serial FDG PET scans are a pre-requisite for individuals with inadequate preliminary EOT FDG PET scans, employed for elucidating therapeutic failures requiring a radio-therapeutic intervention. Consolidation radiotherapy transforms instances of a partial response to a complete response with suitable chemotheraphy. Indicators of prognosis in primary mediastinal B cell lymphoma incorporate parameters such as total lesion glycolysis, metabolic tumour volume and metabolic heterogeneity. Instances of a positron emission tomography (FDG PET) scan with a Deauville score of 1 to 3 are administered rituximab and anthracycline containing regimen and can be further managed with simple observation versus a radiotherapy. Subjects with Deauville score 4 to 5 are managed with the treating physician’s choice per se.\textsuperscript{5,6}

**Relapsed or refractory lymphoma (PMBCL)**

The lymphoma disseminates beyond the mediastinum to metastasize into the liver, pancreas, kidney and central nervous system. Singular
radiotherapy is curative in lesions confined to the mediastinum and in subjects devoid of preceding radiotherapy exposure. Autologous stem cell transplant (ASCT) is adopted following a high dose chemotherapeutic regimen (HDCT) in addition to or devoid of concomitant radiotherapy. Second line therapy incorporates drug antibody combinations such as rituximab with ifosfamide, carboplatin and etoposide (R-ICE) and rituximab with dexamethasone, cytarabine and cisplatin (R-DHAP). Progression free survival (PFS) at 4 years for chemosensitive disease is approximately at 61%.\(^5\)^\(^6\) Targeted therapy utilized in primary mediastinal B cell lymphoma (PMBCL) constitutes of cell surface markers, disrupted cellular signalling and programmed death ligands. Genetic modifications of the programmed death ligand (PDL) situated on genetic locus 9p24.1 amplifies PDL-1 and PDL-2. The aforementioned enhancement is frequent in PMBCL. Therapeutic efficacy of anti CD30 antibody drug conjugate brentuximab vedotin is minimal with an objective response rate (ORR) of 13%. Alternatively, pembrolizumab configures as a humanized monoclonal antibody adhering to PD-1 while deterring the concurrence of PD-1 and PD-1 ligands. Objective response rate (ORR) achieved is at an estimated 41%. Architectural modifications within the 9p24 locus in the lymphoma (PMBCL) induces a dysregulation of JAK/STAT signalling pathway. PMBCL appears contingent to the JAK/STAT network and cellular proliferation is partially inhibited with prohibited JAK2. Efficacy of drug conjugate ruxolitinib as a JAK inhibitor and SB518 as JAK2/FLT3 inhibitor can be assessed with Hodgkin’s lymphoma and primary mediastinal B cell lymphoma. Genetically altered T lymphocytes along with anti-CD19 chimeric antigen receptor (CAR) is efficacious in treating CD19+ B cell lymphoma. It can be applicable as an identical therapy for PMBCL.\(^5\)^\(^6\) Relapsed or refractory instances of PMBCL are managed with rituximab with gemcitabine, vinorelbine and doxorubicin (R-GVD) (Table 1).

Table 1 Modified Ann Arbor Staging for Non Hodgkin’s Lymphoma.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
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<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region or a lymphatic organ (spleen or thymus or Waldeyer ring)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph node regions on the same side of the diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions / structures on both side of the diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Involvement of the extra-nodal sites beyond the designated E.</td>
</tr>
<tr>
<td>E (for stages I to III)</td>
<td>Involvement of the single extra-nodal site contiguous or proximal to the known nodal site</td>
</tr>
<tr>
<td>A or B</td>
<td>Absence (A) or Presence (B) of fever, drenching sweats or loss of &gt; 10% body weight in the preceding six months</td>
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Acknowledgments
None.

Conflicts of interest
The author declares that there is no conflicts of interest.

References