Susceptive, Supplemented, Stockpiled - Follicular Lymphoma

Anubha Bajaj*
Histopathology Unit, A.B. Diagnostics, New Delhi, India

Abstract

Follicular lymphoma may be defined as a B cell non-Hodgkin’s lymphoma where the lymphoid follicles of the neo-plasm may simulate the typical secondary, activated follicles. It comprises of 40% of the adult lymphomas and 22% of the indolent no Hodgkin’s lymphomas of the developed world with greater than 1500 instances of annual prevalence. The disorder is infrequent in Africans and with adolescents (patients below 20 years of age). A nodular lymphocyte predominance Hodgkin’s disease (NLPHD) or a nodal reactive follicular hyperplasia (RFH) may replicate the disorder in children. A majority (80%) of individuals necessitate a therapeutic intervention on account of disease progression. An estimated one fifth (20%) of patients may survive in the absence of therapy for the first decade following detection.

Keywords: Follicular lymphoma; Nodular lymphocyte; Hodgkin’s disease

Introduction

Disease characteristics

Classified by the world health organization (WHO2017) the disorder elucidates [1-3]:

Follicular lymphoma grades 1, 2, 3a and 3b. The variants may depict a non-reactive CD10- with a lack of BCL2- rearrangements and an immune reaction with IRF 4+ and/or MUM1+.

- Follicular lymphoma in situ (FLIS).
- Duodenal type Follicular lymphoma.
- Paediatric type follicular lymphoma.
- IRF 4+ reactive large B cell lymphoma.
- Primary cutaneous follicular centre cell lymphoma.

Follicular lymphoma grading

The contemporary world health organization (WHO 2017) classification categorizes the follicular lymphomas as per the cytological constituents [1,3].

A) Grade 1 is denominated with less than 5% centroblasts per high power microscopic field/(40x).

B) Grade 2 delineates a presence of 5-15 centroblasts per high power field. The distinction betwixt grade 1 and grade 2 may be hypothetical, especially while determining the therapeutic options.

C) Grade 3 a may comprises of one third instances (30%) of follicular lymphomas and may be designated as an emergence of greater than 15 centroblasts per high power field with the concomitant occurrence of centrocytes. Grade 3 b demonstrates a consolidated configuration of centroblasts with a lack of centrocytes.

The follicular lymphoma may be genetically associated with the diffuse lymphoma (DLBCL), though therapeutically managed as the follicular variant. Follicular lymphoma elucidating MUM 1/IRF 4 genetic mutations in the absence of CD10-immune reactivity may be considered an aggressive, high grade variant, frequently with grade 3A or 3B sub-types while implicating the elderly with an accelerated clinical course [4]. These represent a mere 5% of the follicular lymphomas and may lack the IGH/BCL2 rearrangements [2]. Translocation or amplification of BCL 6 may co-exist along with diffuse infiltration of the tumour regions. Follicular lymphoma grade 3 may depict enhanced standardized uptake levels on the positron emission tomography (PET) scan [2].

Histomorphology

A nodular configuration of the lymph node may be exhibited on gross examination and with minimal magnification (10x). As the disease evolves the nodules coalesce into a diffuse countenance [5]. The lymphoma is composed of small and large lymphoid cells. The minute cells of the magnitude of small lymphocytes may delineate minimal, indistinct cytoplasm, irregular, cleaved nuclei with predominant indentations, convolutions and a coarse chromatin. The cells may be designated as germinocytes, centrocytes, poorly differentiated lymphocytes or as small cleaved follicular centre cells [1]. The large cells may be 2-3 times the diameter of the small lymphocytes with a characteristic perimeter of cytoplasm, vesicular nuclei containing 1-3 nucleoli abutting the nuclear membrane and finely dispersed nuclear chromatin. The cells represent the proliferating compartment of the tumour with a rapid multiplication time and may be termed as germinoblasts, centroblasts, histiocytes, large (cleaved or noncleaved) follicular centre cells, large lymphoid cells or lymphoblasts [1]. Bi-nucleated cells akin to the Reed Sternberg cells may be demonstrated. A non-malignant component of follicular centre cells or enlarged cells may also be present within the incriminated lymphoid follicles. Immune reactivity to fascin may be absent [2].

Immunehistochemistry

The follicles of the lymphoma display monoclonal B cells commingled with varying amounts of non-malignant miniature T cells, macrophages with follicular dendritic cells (FDCs) which may be comparable to the germinal centre cells. Pan B antigens such as CD19+, CD20+, CD22+, CD79a+ may be enunciated along with

*Corresponding author: Anubha Bajaj, Histopathologist in A.B. Diagnostics, New Delhi, India, Tel: 00918611653956; E-mail: anubha.bajaj@gmail.com

Received: October 01, 2018; Accepted: December 12, 2018; Published: December 19, 2018

Citation: Bajaj A (2018) Susceptive, Supplemented, Stockpiled - Follicular Lymphoma. Oncol Cancer Case Rep 4: 151.

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human leukocyte antigen (HLA DR) [1,2]. Surface and cytoplasmic immunoglobulin M (Ig M) may depict light chain restriction and the CD10 (CALLA) antigen may be elucidated in 60-70% instances [6]. The infiltrated inter-follicular regions may exhibit numerous CALLA or CD10+ cells, in contradiction to the cellular exudation of reactive follicular hyperplasia. BCL6 + may be immune reactive along with BCL2+ in 85% individuals, whereas BCL2- may be non-reactive with follicular hyperplasia. CD5- and CD43- may not be delineated [1,2].

**Molecular modifications**

The immunoglobulin clones and genetic rearrangements with hyper-numerous and somatic hypermutations may be manifest. Translocation or genetic modification of t (14;18) (q32; q21) may appear in 85% cases. The chromosomal translocation may coexist with the immunoglobulin H (IGH) locus along with the BCL2 gene, thereby inducing a BCL2 over expression (an antiapoptotic molecule situated in the inner mitochondria membrane- the functional capacity of which may be neutralized in non-malignant follicular centre cells) [1,2]. Anomalies within the BCL2 may inhibit the malignant follicle centre cells from apoptosis. Follicular lymphoma essentially emerges from cellular aggregation rather than a cellular multiplication [7]. Rearrangements of the BCL2 in concordance with molecular modifications may distinguish follicular lymphoma from a diffuse lymphoma (DLBCL), a classical follicular hyperplasia, marginal zone lymphoma with a follicular configuration or a mantle cell lymphoma. CD5 and CD23 may appear identical to the resting B cells. On micro array analysis (GEP) may simulate the typical germinal centre and B cell aggregates and 2 follicular lymphomas. The electron microscopy discerns the material to comprise of membrane bound vesicles, electron dense bodies and membranous structures.

The appearance of centric amorphous, acellular, eosinophilic, proteinaceous substance which may be stained by a periodic acid Schiff’s (PAS +) stain, may be demonstrated in grade 1 and 2 follicular lymphomas. The electron microscopy discerns the material to comprise of membrane bound vesicles, electron dense bodies and membranous structures.

**Clinical elucidation**

The lymphoma evolves gradually in the adults though it may be incurable. Majority of the individuals present with disease stage III or IVa. Grade I follicular lymphomas may be asymptomatic with a generalized disease, a favourable outcome and an appearance in extra-nodal locations such as liver and bone marrow. Grade 3 follicular lymphomas may be confined or restricted at the preliminary stage with an aggressive behaviour and a gradual disappearance of nodular configuration to eventually become diffuse. Grade 2 follicular lymphomas depict clinical features betwixt grade 1 and grade 3, though it may frequently simulate grade 1. Thus grade 1 and grade 2 may be defined as low grade follicular lymphomas. Grade 3 follicular lymphoma may predominantly be composed of mammoth cells and is consequently incorporated with the high-grade lymphomas [1]. Lymphomas comprising of small cleaved and mixed cells may elucidate a prognosis simulating that of a purely follicular or follicular and diffuse lymphoma [10]. Large cell lymphomas or lymphomas with a mixed follicular and diffuse configuration may display a poorer outcome than purely follicular lymphoid articulations [1]. The extra nodal arrangement of the lymphoma may involve the B cell dependent regions of the spleen with eccentric foci within the white pulp. The liver may display a peri-portal lymphoid infiltrate while the bone marrow has a para-trabecular mode of extension. The expansile dermal permeation of the lymphoma may be independent of the blood vessels or skin adnexa [11]. Follicular lymphoma grade 1 may appear in the peripheral blood with the cells displaying a prominent nuclear cleft, which may be designated as “butock cells” [1]. The blastic or blastic transformation with the aggressive forms of follicular lymphoma, where the tumour cells may mimic a Burkett’s lymphoma or a lymphoblastic lymphoma may be delineated. A large cell lymphoma with anaplastic or pleomorphic CD30+ cells may also be exemplified [1].

**Diverse morphologies of follicular lymphomas**

1. Fine or coarse fibrous trabeculation within the lymphoma may highlight the nodular configuration so that the tumour resembles an epithelial malignancy. The feature may be frequently elucidated in the grade 3 follicular lymphomas or with retro-peritoneal, mediastinal and cervical lesions.

2. Monocytoid B cells with permeation into the marginal zone may appear roughly 10% lymphomas. Aggregates of monocytoid B cells may circumscribe the tumour follicles. The monocytoid B cells and the follicle centre cells may arise from an identical cellular clone. The appearance of monocytoid B cells may be accompanied by an increased mortality [1].

3. The appearance of centric amorphous, acellular, eosinophilic, proteinaceous substance which may be stained by a periodic acid Schiff’s (PAS +) stain, may be demonstrated in grade 1 and 2 follicular lymphomas. The electron microscopy discerns the material to comprise of membrane bound vesicles, electron dense bodies and membranous structures.

4. Mammoth eosinophilic globules or collective immune globulins or a singular vacuole within the cytoplasm, may laterally displace the nucleus to elucidate a signet ring appearance [1].

5. A distinct differentiation towards plasma cells may arise within the malignant follicles.

6. Cells exhibiting cerebriform nuclei (simulating a T cell lymphomas) or with multi-lobular nuclei may be encountered.

7. The tumour follicles may be percolated with miniature, round, mantle zone lymphocytes, thus conferring a progressively transformed germinal centre (floral variant) like appearance to the follicles.

8. Rosettes may be articulated by the cytoplasm and cytoplasmic extensions of lymphoid cells, thus resembling the neuroendocrine cell component.

9. Hyaline vascular follicles, simulating the hyaline vascular variant of Castleman’s Disease, may emerge.
10. The designated reverse or inverse variant of follicular lymphoma may depict a reversal of staining configuration of the tumour follicles on low power. Thus the follicles may appear dark and intensely stained, in contrast to the lymphoid perimeter.

11. The follicular lymphoma may predominantly depict epitheloid cell granulomas [1].

12. Foci of lymph node within paraffin embedded sections may display retained reactive germinal centres, which may signify a limited stage lymphoma (Figures 1 to 14).

Figure 1: Follicular lymphoma with cortico-medullary follicles.

Figure 2: Follicular lymphoma with fibrous bands demarcating centrocytes.

Figure 3: Follicular lymphoma with homogeneous follicles and absent reaction centres.

Figure 4: Follicular lymphoma-prominent nodules with fibrous banding.

Figure 5: Follicular lymphoma-effaced lymph node architecture with nodular replacement.

Figure 6: Follicular lymphoma with admixed centrocytes and centroblasts-grade II.

Germinal centre morphogenesis

The lymphoma may demonstrate a proliferation of the follicular centrocytes, centroblasts and dendritic reticulum cells. The cellular component depicts a B cell immune phenotype such as the presence of CD20+, CD19+, CD79a+ CD10+ with BCL2- and BCL6- genes, immunoglobulin molecules Ig M, IgG, IgA, and a nonreactive CD3- and CD5-. The genetic typing of the tumour may depict modifications of the BCL2/JH or IGH/BCL2 locus, translocation t (14:18) with somatic mutations of the VH regions [2]. The germinal centre appears initially as a naïve B cell zone, the lymphocytes of which may migrate to the marginal zone or remain within a germinal centre [13]. The B
cell may undergo apoptosis or may passively transform into a memory B cell or the naïve B cells may persevere without metamorphosis whereby a follicular lymphoma may ensue. The recombinant V gene may combine with the expansive clone of B cells along with the somatic hypermutation and genetic class switching, in order to initiate the B cell differentiation [2]. A non-reactive BCL2- on immune staining may emerge on account of mutations within the BCL2 epitope. Thus, application of adjunctive genetic clones of E-17 or SP 66 may be advantageous.

Host immunity in follicular lymphoma

Follicular lymphoma exhibits a fluctuating clinical countenance with exacerbations and remissions. Acute viral illness or a vaccine inoculation may depict a quick, spontaneous or a persistent amelioration of the condition. Therapy with anti-idiotype molecules may be effective in the immune responsive patients, though the immune refractory individuals may not be alleviated. The tumour microenvironment may influence the survival of the patients of follicular lymphoma. The genes impacting B cell differentiation such as the PRKCD, ALDH2, TERF2, NLK, NANS, FBXO 10, SIAH2, PAG etc along with genes affecting the immune response 1 such as LEF 1, CD3Z, ITK, TRD, STAT 4, TBC1D4, BIN2, SKI, INPP1, MYCL1, TEAD 1, ACTN1, IL7R, BIN2, LGALS2, FMOD, TEAD 1, NFIC, JAM3, C1RL, Palladin etc. may be elucidated. Thus immune response 1 with a favourable outcome
may delineate abundant genetic manifestation within the peripheral blood T lymphocytes [2]. Genetic expression associated with immune response 2 may exemplify LGMN, TLR5, C1QA, SEPT10, ME1, MITF, NDN, C4A, C4B, C1QB etc. and may further be accompanied with the specified genetic enunciation within the peripheral blood monocytes and a worse prognosis. However, the applicability of immune response signatures and relevant biomarkers may not be beneficial in routine clinical practice [2]. Follicular lymphoma may exhibit a prognosis arising of a multi-factorial aetiology. Analytical compilations of the risk proliferation index, the tumour grade, the disease stage, the FLIPI index, the host immune reaction or the microenvironment and the mutational profile (m 7-FLIPI) may be mandated [2].

**Histological evolution of follicular lymphoma**

Accessory modification of the follicular lymphoma may ensure a variegated tumour histology and phenotype, accompanied with the BCL2 mutation and a clone specific affiliation to follicular lymphoma.

- The most frequent emergence may be of a diffuse lymphoma (DLBCL)
- A high grade, double hit B cell (HGBCL-DH) lymphoma with MYC, BCL2 and/or BCL6 genetic mutations may be demonstrated [2].
- Pre-B lymphoblastic lymphoma/leukaemia may be exemplified
- A classical Hodgkin’s Lymphoma may appear.
- Histioytic and dendritic cell sarcoma may arise with a progressive follicular lymphoma.

- TP53 mediated metamorphosis of the follicular lymphoma may depict a conversion to a diffuse (DLBCL) lymphoma with elucidation of BCL2+ and MIB 1+ reactivity [2].

Follicular lymphoma may lack the MYC – rearrangements whereas the diffuse (DLBCL) lymphomas may express the MYC+ modifications. The diffuse (DLBCL) lymphomas may exclusively react to the MYC+ protein and may elucidate a c MYC recombination. Follicular lymphoma and the diffuse (DLBCL) lymphomas may display a BCL2 rearrangement. The co-existing BCL2 and MYC rearrangements may signify a high grade, double hit (HGBL-DH) lymphoma [2].

The follicular lymphomas may signify a lymphoblastic metamorphosis with the elucidation of a precursor B cell phenotype which may immune react to TdT+. The bone marrow and the peripheral blood may be implicated with a clinical exponent resembling an acute lymphoblastic leukaemia (ALL). A clone specific analogy to follicular lymphoma may be analyzed with translocation t (14;18). The variant may exemplify a c MYC rearrangement, though it may not be a component of the “double hit” lymphomas enlisted with the world health organization (WHO- DH). Low grade follicular lymphomas may perpetuate locally within the bone marrow and lymph nodes. The variant may elucidate a µ micro-protein + and a non-reactive or a weak BCL2 – [2].

**Follicular lymphoma - in situ (FLIS)**

As defined by the world health organization (WHO, 2017), an in situ follicular lymphoma may be a focal and circumscribed tumour confined to the follicles with an immune reaction to BCL2+. The B cell follicular lymphoma may congregate within and respond to the germinal centre microenvironment. The variant may be determined within 2-3% of the lymph node biopsies and may occasionally coincide with accessory B cells. The genetic anomalies apart from the BCL2 rearrangement may be minimal. The probability of developing a follicular lymphoma may be less than 5%. Therapeutic management may not be required [2].

**Duodenal type of follicular lymphoma**

The variant manifests an immune phenotype and genetic modifications identical to the follicular lymphoma of the lymph nodes such as the BCL2 and IGH recombination, although immune reactivity to IgA + may be manifest. Apart from the aforementioned genetic anomalies, adjuvant aberrations may be minimal. The disorder frequently appears in the duodenum along with accessory locations such as the distal small bowel. Superficial polypoid mucosal lesions may erupt. The intestinal lymphocytes may depict homing receptors such as the α4β7 integrin. Activation induced cytidine deaminase (AID) function may be lacking. The disorder of a restricted emergence may depict amelioration and localized recurrences with an absence of tumour dissemination. The lymphoma may be immune reactive for BCL2+ and CD10+ with an absence of CD3- [2].

**Paediatric follicular lymphoma**

The variant is exceptional (1-2%) and arises in children. Organs such as tonsils, nasopharynx, gastrointestinal tract, testis or lymph nodes may be implicated. The lymphoma may characteristically be high grade (3A/3B). Males are frequently involved (M>>F: 10:1), with a predominant male: female ratio. A majority (85%) of the instances may be confined with stage I and stage II disease at detection. The nodal and extra-nodal configurations of the lymphoma may not be appropriately elucidated [2]. The lymphoma categorized within the head and neck
lymph nodes may belong to stage I. Rearrangements of BCL 2 and/or BCL6 may be absent. The lymphoma typically exemplifies reactivity for CD10+, BCL6+ with an absent immune reaction for BCL2- and MUM1-(2). Organs such as the tonsil or Waldeyer’s ring when involved, may manifest an analogous male: female (M:F) ratio. A concomitant elucidation of MUM 1, BCL 6 andCD10 may be encountered. A cleavage at IRF4 (6p25) may be frequent [2].

i) The IRF 4+ large B cell lymphoma may be categorized as a conditional entity with the contemporary WHO classification. Paediatric testicular, follicular lymphomas may exemplify a stage 1 disease with favourable prognosis and may be reactive to CD10+ and BCL 6+ with a lack of BCL2- and MUM1-reaction. Infrequent cleavage within the BCL6 oncogene may be elucidated. Paediatric follicular lymphomas may display a clone specific germinal centre B cell multiplication of indeterminate malignant capability. The mean age of presentation varies from 15-18 years with infrequent lesions beyond 40 years. Clonally rearranged CD10+ B cells may be delineated with flow cytometry. Immunoglobulin recombination as detected by the polymerase chain reaction (IG PCR +) may be demonstrated. Genetic aberrations may be lacking in the BCL2, BCL6 and/or IRF 4 molecules (2). A consistent complete remission (CR) may be achieved following adequate surgical excision without extended chemo/mono therapy. Thus a conservative therapeutic option may be recommended. Immunoglobulin D (Ig D) may be elucidated at the follicular perimeter along with CD79a+ and CD10+ immune phenotypic cells.

ii) Paediatric type - Nodal follicular lymphoma may elucidate reoccurring mutations within the entire genome. Mutations within TNFRSF14 with concurring copy number neutral loss of Ip 36 may be exhibited in greater than half (>50%) the instances. KMT2D (MLL2) mutation may appear in roughly 16% individuals. These genes may also be modified with the “classic” follicular lymphoma, although with dissimilar percentages. Mutations within the MAPK pathway may be common with MAP2K 1 in half (=50%) the instances or infrequently an RRAS: MAPK 1 mutation may appear [2].

Discussion
Therapeutic protocols
Grade 3 follicular lymphoma may manifest dubitable treatment strategies in concordance with adjunctive follicular or diffuse large B cell lymphomas. Persistent amelioration of diffuse lymphomas (DLBCL) with varying treatment outcomes may also be analyzed. However, the ensuing follicular lymphoma international prognostic index 2 (FLIPI 2) following the employment of rituximab may not be incorporated with the lymphoma grade amidst the various, predominant prognostic factors affecting survival [14]. The optimal employment of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R CHOP) for grade 3 follicular lymphomas may express an objective response rate (ORR) of 100% with a 3-year progression free survival (PFS) survival benefit of 70%. The minimal requirement of a reduced progression free survival (PFS) survival may manifest as greater than 4 lymph node sites with co-existing B symptoms (fever, night sweats, weight loss >10% of the body weight) [5]. Evolution to a diffuse lymphoma (DLBCL) may exemplify an increase in the international prognostic index (IPI) score with elevated lactic dehydrogenase (LDH). Acute Myeloid Leukaemia may appear in patients beyond 60 years at the commencement of therapy. Rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R CHOP) may be efficacious in grade 3 follicular lymphoma with an enhanced progression free survival (PFS) and a prognosis concordant with the limited stage of diffuse lymphoma (DLBCL). The exclusion of a frank conversion to a diffuse lymphoma (DLBCL) may be a pre-requisite prior to the initiation of treatment. The geriatric patients may necessitate the employment of adjunctive therapeutic options. The optimal implementation for rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) in grade 3 follicular lymphoma may require concordant favourable aspects as such [15,16] (Table 1).

- Age beyond 60 years.
- Male sex.
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) greater than 1.
- Stage 3 or 4 with Ann Arbor classification.
- More than four incriminated lymph node sites.
- Bulky disease beyond 6-centimetre magnitude
- More than a solitary, implicated extra-nodal site.

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<tr>
<th>Follicular Lymphoma</th>
<th>Reactive Follicular Hyperplasia</th>
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<tbody>
<tr>
<td><strong>Architecture</strong></td>
<td><strong>Preservation of nodal architecture</strong></td>
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<tr>
<td>Even distribution of follicles throughout cortex and medulla</td>
<td>Follicles more prominent in cortical portion of lymph node</td>
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<tr>
<td>Slight or moderate variation in size and shape of follicles</td>
<td>Marked variation in size and shape of follicles with presence of elongated, angulated and Dumbbell shaped forms</td>
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<tr>
<td>Fading of follicles</td>
<td>Sharply demarcated reaction centres</td>
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<tr>
<td>Massive infiltration of capsule and peri-capsular fat with or without formation of malignant follicles outside capsule</td>
<td>Nil or moderate infiltration of the capsule or peri-capsular fat with inflammatory cells that may be arranged as focal or peri-vascular aggregates(when accompanied with lymphadenitis)</td>
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<tr>
<td>Condensation of reticulin fibres at the periphery of the follicles</td>
<td>Little or no alteration of the reticular framework</td>
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<th>Cytology</th>
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<td>Follicles composed of malignant cells exhibiting cellular pleomorphism with nuclear aberrations.</td>
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<td>Lack of phagocytosis</td>
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<td>Relative paucity of mitotic figures usually without significant differences inside and outside the follicles, presence of atypical mitosis</td>
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<tr>
<td>Analogy of cell type inside and outside the follicles</td>
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Table 1: Allegory of reactive/lymphoid neoplasm follicles [1].
• Bone marrow involvement.
• The appearance of B symptoms.
• International Prognostic Index (IPI) of the range 3 or 4.
• Follicular Lymphoma International Prognostic Index (FLIPI) of the magnitude 3 to 5.
• Haemoglobin values of 12 g/dL.
• Lactic dehydrogenase (LDH) levels beyond upper limit of normal.
• β2 micro-globulin levels beyond 4 mg/L.

Conclusion

Radiotherapy may be employed as an accessory treatment modality particularly within the lymph nodes and the incriminated drainage areas or with the implicated organs with specified lymph node drainage. A computerized tomography (CT/PET) or a positron emission tomography in conjunction with the enunciated Ki 67 subsequent to the initiation of chemotherapy, may be evaluated at mid therapy [12]. Therapeutic outcomes may be analysed by the physical examination, complete blood counts, serum lactic dehydrogenase (LDH) values and a computerized tomography (CT) and/or a positron emission tomography (PET CT) imaging. A complete response (CR) may be investigated by performing a bone marrow aspiration and biopsy. The therapeutic response may be categorized by the foundation laid by the international working group. A type II anti CD20 monoclonal antibody obinutuzumab may be employed to enhance the efficacy of rituximab. A non-apoptotic cell demise may ensue with a diminished complement activation. Amplified direct cell dissolution, antibody dependent cell mediated cytotoxicity along with a B cell elimination from whole blood and lymphoid tissues may ensue. Relapsed or refractory follicular lymphoma may appropriately be managed by obinutuzumab with cyclophosphamide, doxorubicin, vincristine and prednisone (G CHOP) elucidating an objective response rate (ORR) of 96% or with cyclophosphamide in combination with fludarabine and obinutuzumab with a manifested objective response rate (ORR) of 93%.

References

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