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Case Report

Primary cervical and uterine corpus lymphoma; a case report and literature review

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Abstract: Primary lymphoma of the uterine corpus and cervix is rare. We present a case of primary non-Hodgkin follicular lymphoma isolated to uterine corpus and parametria with focal spread to ovaries and fallopian tubes, incidentally found on the background of endometrial malignancy. A summary of the published cases focusing on the presentation and prognosis as well as a review of current management are discussed. The rising incidence of extra-nodal lymphoma and recent changes in classification and therapeutic approach, require clinical vigilance. In the absence of prospective studies assessing the value of the available therapeutic options, data from retrospective series and scattered case reports are presented in this review.

Keywords: Non-Hodgkin's lymphoma, extra-nodal lymphoma, uterine/cervical lymphoma

Introduction

Lymphoma is the commonest haematological cancer and is divided into Hodgkin (20-30%) and non-Hodgkin (70-80%). Non-Hodgkin Lymphoma (NHL) is diverse and often subdivided into aggressive and less aggressive forms [1]. Aggressive NHL includes diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma (PTCL), Burkitt's lymphoma, mantle cell lymphoma (MCL) and AIDS-related lymphoma. The most common tumour site is the neck, but they can occur at other sites too. Usually by the time of diagnosis the disease is widespread with systemic symptoms. DLBCL is the most common NHL and accounts for about 30% of new cases. Less aggressive NHL includes follicular lymphoma, which accounts for 22% of new cases. These have a slow progression rate with median survival periods of up to 10 years. Clinical presentation can vary widely and treatment is not always required. Watchful waiting until symptoms develop is often the best option [1].

The incidence of extra nodal NHL is rising [2]. In up to 90% of NHL patients, the disease has spread by the time of diagnosis and cure rates are lower compared to localised disease. Patients with extra-nodal forms of NHL usually present to, and are initially treated by, specialists who deal with that particular body system [1]. Isolated genital tract extra–nodal disease accounts for less than 1% of NHL [3]. In a series of 147 isolated genital tract NHL the percentage breakdown was as follows: 59% ovarian, 15.5% uterine corpus, 11.5% uterine cervix, 7.5% vulval and 6% vaginal. The rest of the cases involved more than one organ [4]. In up to 80% of cases, uterine and cervical NHL appear to be the primary site of disease [4]. The most common subtype is DLBCL with follicular lymphoma in second place. Gynaecologists should be familiar with the features of isolated genital tract NHL, as patients can experience delay in diagnosis and misdiagnosis. Accurate histopathological typing of this heterogeneous disease is necessary to guide management. This report describes a case primary NHL of uterine corpus with a focal spread to the fallopian tubes and ovaries but sparring of the cervix. We also present an update of reported cases and recent therapeutic trends.

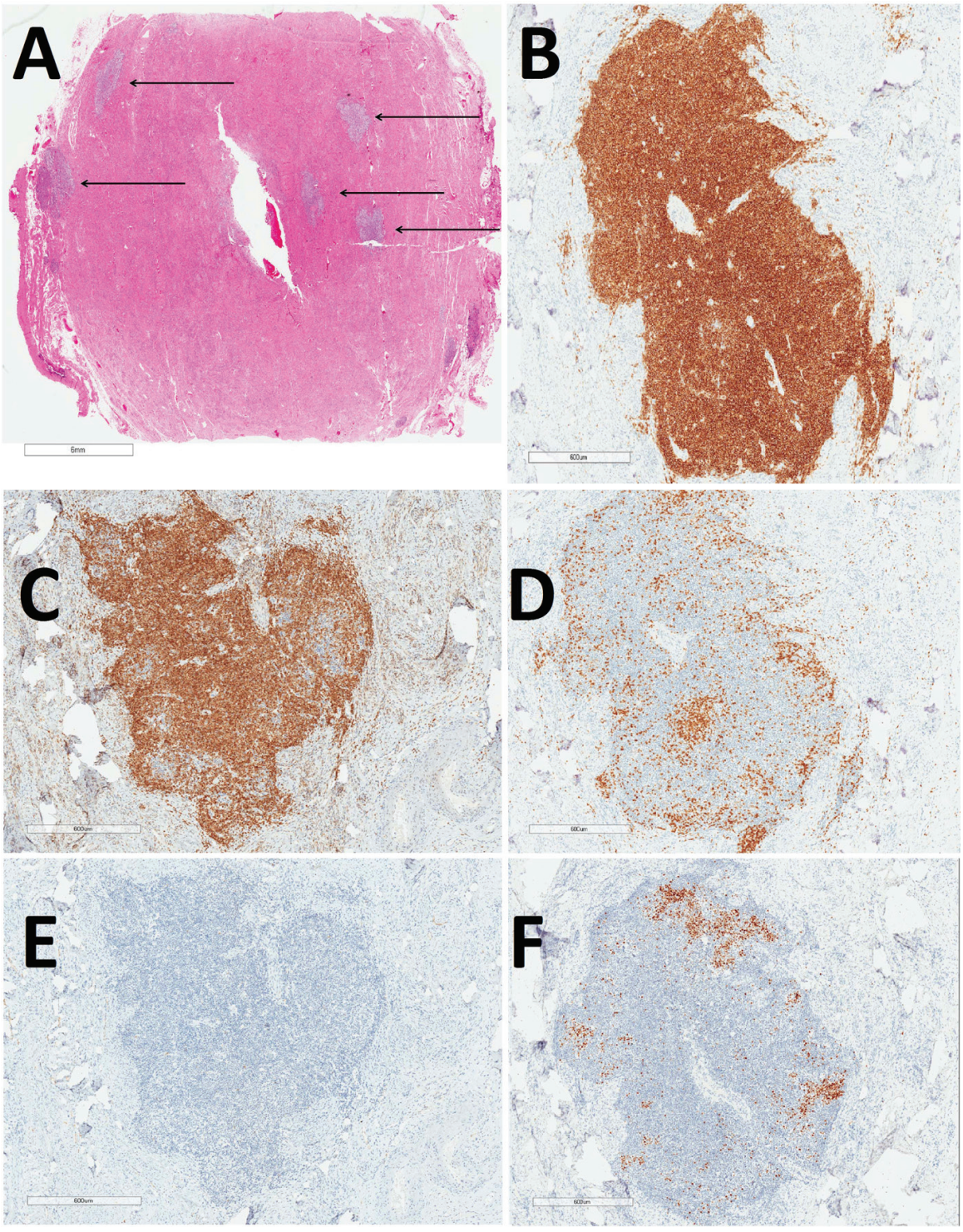

Figure 1. Immunohistochemical analysis suggested the soft tissue manifestation of low grade follicle centre lymphoma, in addition to a FIGO Grade 2 stage IA endometrioid adenocarcinoma with villous papillary architecture. A. The uterus contains atypical lymphoid aggregates in the myometrium (shown with arrow) – x0.4 magnification, haematoxylin-eosin stain. Scale bar: 6mm. B. Immunohistochemical staining reveals the lymphoid aggregates strongly express CD20 - x4 magnification. Scale bar; 600um. C. They are positive for BCL-2 - x4 magnification. Scale bar: 600um. D. CD3 highlights the reactive T-cell population – x4 magnification. Scale bar: 600um. E. CD10 was negative in this case however – x4 magnification. Scale bar: 600um. F. The Ki-67 growth fraction was low, around 5% - x4 magnification. Scale bar: 600um.

Case

A 65-year old multiparous asymptomatic woman had an incidental finding of an endometrial polyp on pelvic ultrasound scan, as part of UK CTOCS (UK Collabarative Trial of Ovarian Cancer Screening) study. Subsequent hysteroscopy confirmed the presence of a small fundal polyp and curettage was performed. Histology of these curettings showed a grade 2 endometrioid adenocarcinoma with villous and papillary features. A total laparoscopic hysterectomy and bilateral salpingoophorectomy with unremarkable intraoperative findings followed.

Histology showed a normal size uterus, infiltrated with a fundal endometrial adenocarcinoma tumour measuring 10 x 10 x 6mm. Myometrial invasion was less than 50%, nearest distance to serosa 11mm, and no cervical or lymphovascular space invasion was present. Cervix, uterus, parametria, both fallopian tubes and ovaries all contained scattered dense infiltrates of small monomorphic atypical lymphocytes (**Figure 1A**). Foci of lymphoma were present in both ovaries and fallopian tubes. Immunohistochemistry revealed atypical lymphocytes that stained positive for CD20 (**Figure 1B**) and BCL2 (**Figure 1C**), and CD3 (**Figure 1D**). They were negative for CD5, CD23, CD10 and cyclin D1 (**Figure 1E**). The Ki-67 growth fraction of the tumour cells was low approximating 5% (**Figure 1F**). Appearances suggested the soft tissue manifestation of low grade follicle centre lymphoma, in addition to a FIGO Grade 2 stage IA endometrioid adenocarcinoma with villous papillary architecture.

Staging with CT of thorax abdomen and pelvis showed no lymphadenopathy or other organ involvement, while LDH levels were normal at 384U/L. With an Ann Arbor stage of IE and no symptoms the haematologist withheld further treatment. At 15 months of follow up the patient remains well.

Methods for the clinical case analysis

Ethical statement

Experiments involving human subjects were done in accordance with the Helsinki Declaration of 1975 and in accordance with the relevant ethical and legal standards established and accepted by the host institution. Accordingly, in the case which is herein presented, informed signed consent has been obtained by the patient.

Imunohistochemistry

Four micrometers (μm) sections were cut from the FFPE blocks; all sections were cut using the same microtome and stained within 24 hours. Slides containing the sections were baked in an oven at 50°C overnight. PT link tanks (Dako, Glostrup, Denmark) were used to perform deparaffinisation and heat-induced epitope retrieval (EnVision FLEX Target Retrieval Solution High pH; Dako). All slides were incubated for 20 minutes at 97°C and left in buffer (EnVision FLEX wash buffer; Dako) at room temperature for a minimum of 5 minutes to cool down. Staining was performed using an automated immunostainer (AutostainerLink 48; Dako). The protocol was as follows: all slides were incubated for 5 minutes in an endogenous block (EnVision FLEX peroxidase-blocking reagent; Dako) and then incubated with primary antibody for 30 minutes. Where appropriate, this was followed by a 15 minute incubation step to amplify the signal (EnVision FLEX+ mouse (linker); Dako). All slides had 20 minutes' incubation in labelled polymer (EnVision FLEX /HRP; Dako). Each individual stage was followed by buffer rinses (EnVision FLEX wash buffer; Dako). Staining was visualised using the chromogen DAB (3, 3' Diaminobenzidine) for 10 minutes, counterstained with haematoxylin (EnVision FLEX; Dako) for 5 minutes and manually coverslipped (Surgipath, UK) with mounting medium (Dako). Primary antibodies: CD20 (1:1, Dako), BCL2 (1:500+, Dako), CD3 (1:1, Dako), CD21 (1:20+, Dako), CD23 (1:200, Leica, Wetzlar, Germany), CD10 (1:20+, Leica).

The slides were digitally scanned using an Aperio Scanscope CS at varying resolution and digital images were captured.

Literature review

In 2001 Renno et al published a review of 16 cases of primary uterine corpus lymphoma [5]. Dursun et al in 2005 reviewed 31 reported cases and Korcum et al in 2007 published a review including 56 cases of lymphoma of cervix [6, 7]. Hariprasad et al in 2006 reviewed the literature and summarised results from 90 cases and in the same year Frey et al also pub-

Table 1. Overview of the reported cases of primary cervical lymphoma. Features of clinical presentation, histological classification and Ann-Arbor staging for each case are presented. The combination oftherapeutic modalities with the resulting outcome for each case is noted along with the duration of follow up

Reference	Age	Clinical Presentation	Histologic type	Stage (Ann-Arbor)	Treatment	Outcome	Follow up (months)
Wan-Ting Huang et al. 2005 [22]	42	Pain	Burkitt's	IE	Hyst	DOD	0
Goker et al. 2005 [23]	55	Pain	Burkitt's	IE	ChT	NERD	14
Semczuk et al. 2006 [24]	43	NO	BCL	IE	TAH/ChT	NERD	10
Lorusso et al. 2007 [13]	29	PVB	LBCL	IE	Cone/ChT	NERD	60
Signorelli et al. 2007 [25]	54	n/a	DLBCL	IE	TAH-BSO	NERD	118
	58	n/a	DLBCL	IE	TAH-BSO/ChT	NERD	228
	33	n/a	DLBCL	IIE	TAH-BSO/ChT	NERD	227
	45	n/a	DLBCL	IE	ChT/TAH-BSO	NERD	38
	44	n/a	DLBCL	IIE	ChT/TAH-BSO	NERD	84
	32	n/a	DLBCL	IE	ChT	NERD	91
	56	n/a	DLBCL	IIE	ChT	NERD	168
	29	n/a	DLBCL	IIIE	ChT	NERD	130
Hanprasertpong et al. 2008 [26]	25	PVB	DLBCL	IE	ChT	NERD	29
Okudaira et al. 2008 [27]	68	PVB	DLBCL	IIE	ImT-ChT/RT	NERD	5
Ustaalioglou et al. 2009 [28]	65	B	DLBCL	IEB	ImT-ChT/RT	NERD	10
Amna et al. 2009 [29]	46	PVB	Follicular	IE	ImT-ChT/RT	NERD	12
Upanal et al. 2011 [30]	51	Pain/PVB	DLBCL	IIE	ImT-ChT/RT	NERD	19
Kanaan et al. 2012 [31]	80	Pain	DLBCL	III	ChT	DOD	n/a
Binesh et al. 2012 [32]	85	PVB	DLBCL	IE	ImT-ChT/RT	DOO	5
Vasudev et al. 2012 [33]	52	PVB	DLBCL	IE	Rad Hyst	NERD	20
Calli et al. 2012 [34]	65	PVB	DLBCL	n/a	ChT-ImT	NERD	n/a
Parnis et al. 2012 [35]	54	PVB	DLBCL	IE	ImT-ChT/RT	NERD	2

PVB: Per Vagina Bleeding, ImT: ImmunoTherapy, ChT: ChemoTherapy, RT: RadioTherapy, Sx: Surgery, Hyst: Hysterectomy, TAH: Total Abdominal Hysterectomy, Rad: Radical, BSO: Bilateral Salpingo Oophorectomy, PLD: Pelvic Lymphnode Dissection, UAE: uterine artery embolization, TCRBCL: T-Cell Rich B-Cell Lymphoma, PTCL: Peripheral T Cell Lymphoma, DLBCL: diffuse large B-cell lymphoma, MCL: Mantle Cell Lymphoma, MZBCL: Marginal Zone B Cell Lymphoma, NERD: no evidence of recurrent disease, DOO: Died of other causes, DOD: Died of disease, Rec: Recurrence, IWF: L/I/H: International Working Formulation Low/Intermediate/High grade.

lished a review of 61 cases of lymphoma of cervix and uterine corpus [8, 9]. Kosari in 2005, reported 6 uterine and 10 cervical primary lymphoma cases in a large series, which we did not include in our results due to difficulty in extracting individual information [4]. We collated the reported cases from the aforementioned publications, removed the duplicates and added the ones found by our own literature search who were not included in the above reviews. We then updated the results with cases published until December of 2012. The total number of cases of primary uterine corpus and cervical lymphoma resulted in 178. Two tables, one for cervical and one for uterine corpus lymphoma were prepared including information collected from full text and abstracts of eligible cases. Accordingly, in **Tables 1** and **2**, we present the cases to date, without those reported in the above mentioned case series.

Results

The 178 cases collected included 118 cervical and 60 uterine primary NHL. For the cervical lymphomas the median age of presentation was 46 years (range 20-85 years), and the most common histological type was DCBCL (37%). Only 5% of the cases described were follicular NHL. The Ann Arbor stage at presentation was I in 69.2%, II in 22.7% and III and above in 8.1% of patients. Treatment included surgery

Table 2. Overview of reported cases of primary uterine corpus lymphoma. Features of clinical presentation, histological classification and Ann-Arbor staging for each case are presented. The combination of therapeutic modalities with the resulting outcome for each case is noted along with the duration of follow up

Reference	Age	Clinical Presentation	Histologic type	Stage (Ann-Arbor)	Treatment	Outcome	Follow up (months)
Trenhaile et al. 2001 [36]	66	PVB	DLBCL	IIE	ChT/RT	NERD	25
Murdoch et al. 2001 [37]	52	n/a	PTCL	IE	TAH-BSO/ChT	NERD	33
Olde Scholtenhuis et al. 2002 [38]	78	PVB	DLBCL	IE	TAH	Rec	84
Iyengar et al. 2004 [39]	65	n/a	MZBCL	IE	TAH-BSO	n/a	n/a
	29	n/a	DLBCL	IE	ImT-ChT	NERD	4
Rittenbach et al. 2005 [40]	44	PVD	DLBCL	IE	TAH	NERD	36
Agaoglu et al. 2005 [41]	68	n/a	DLBCL	IEB	TAH-BSO/ChT	NERD	41
	47	PVB	DLBCL	IE	ChT/RT	NERD	13
Keller et al. 2006 [42]	40	PVB	Burkitt's	IE	ChT/Hyst	NERD	10
Shen et al. 2007 [43]	68	Pain/PVB	PTCL	IEB	TAH-BSO	n/a	n/a
Egyed et al. 2007 [44]	26	PVB	DLBCL	IE	ImT-ChT	NERD	9
Ab Hamid et al. 2008 [45]	43	PVB	DLBCL	IE	ChT	AWD	n/a
Lemos et al. 2008 [46]	89	n/a	DLBCL	IE	Sx	DO?	5
Leung et al. 2008 [47]	60	PVB	DLBCL	IE	ImT-ChT	NERD	28
Heeren et al. 2008 [48]	61	n/a	MZL	IE	Sx	NERD	8
Su et al. 2008 [49]	69	PVB	DLBCL	IE	TAH-BSO/ImT-ChT	NERD	36
Rajnics et al. 2009 [50]	26	PVB	DLBCL	IE	ImT-ChT	NERD	60
	45	PVD	DLBCL	IE	ImT-ChT	NERD	48
Samama et al.2011 [51]	79	Urinary obstruction	DLBCL	n/a	ImT-ChT	DOO	9
Parva et al. 2011 [52]	21	PVB	DLBCL	IE	ImT-ChT	NERD	72
Upanal et al. 2011 [30]	49	PVB	DLBCL	IE	ImT-ChT/RT	NERD	20
This Case	65	NO	Follicular	IE	TLH-BSO	NERD	15

PVB: Per Vagina Bleeding, ImT: ImmunoTherapy, ChT: ChemoTherapy, RT: RadioTherapy, Sx: Surgery, Hyst: Hysterectomy, TAH: Total Abdominal Hysterectomy, Rad: Radical, TLH: Total Laparoscopic Hysterectomy, BSO: Bilateral Salpingo Oophorectomy, PLD: Pelvic Lymphnode Dissection, UAE: uterine artery embolization, TCRBCL: T-Cell Rich B-Cell Lymphoma, PTCL: Peripheral T Cell Lymphoma, DLBCL: diffuse large B-cell lymphoma, MCL: Mantle Cell Lymphoma, MZBCL: Marginal Zone B Cell Lymphoma, NERD: no evidence of recurrent disease, DOO: Died of other causes, DOD: Died of disease, Rec: Recurrence, AWD: Alive with disease, IWF: L/I/H: International Working Formulation Low/Intermediate/High grade.

in 42% of cases. In 9.2% surgery was the only mode of treatment, with 16.8% having chemotherapy only, 10.9% radiotherapy only, and the rest having multimodal treatment. Rituximab was used in 11.7% of the cases. In 85.2% of patients there was no evidence of recurrence within a median follow up time of 40.5 months (range 2-240 months). Recurrence is documented in 2% of patients within 12-48 months, while 8.6% died of their disease within 0-40 months.

For the uterine lymphomas the median age of presentation was 54 years (range 21-89 years), and the most common histological type was DCBCL (56%). The Ann Arbor stage at presentation was I in 71.6%, II in 13.3% and III and above in 15.1% of patients. Treatment included surgery at 58.3% of cases and surgery was the only mode of treatment in 21.6%, with 23.3% having chemotherapy alone and the rest having multimodal treatment. Rituximab was used in 18.3% of the cases. In 53.3% of patients there was no evidence of recurrence within a median follow up time of 33 months (range 4-108 months), while in 26.6% of patients follow up data were not available. Recurrence occurred in 5% within 84 months, while 11.6% died of disease within 1-120 months.

Discussion

The predominant presentation of isolated genital tract extra-nodal NHL is dysfunctional uter-

ine bleeding, followed by presence of cervical or pelvic mass and pain. Absence of symptoms can also be the case in early stages while systemic 'B' symptoms are rare.

Suggestive MRI findings of uterine corpus lymphoma are diffuse infiltration of uterine corpus and cervix without disruption of the epithelial layer and homogeneous signal intensity of the lesion. For the lymphoma of cervix, lack of mucosal involvement, and sparing of stroma and uterine junctional zone seem to be unique characteristic [9]. Cervical cytology may show dyskaryosis, but is rarely diagnostic for this stromal neoplasia. Even after biopsy of sub epithelial tissues the diagnosis of benign lymphoid aggregates which are common in this area needs to be excluded. Endometrial biopsy could suggest the diagnosis, but the differential diagnosis of poorly differentiated carcinoma, endometrial stromal neoplasms, melanoma, and inflammatory conditions such as reactive lymphoid infiltrates needs to be considered.

Staging includes peripheral blood tests (Full Blood Count and blood smear, LDH), biopsies (bone marrow, lymph nodes, affected organs) and CT imaging (neck, chest, abdominal and pelvis). The use of Positron Emission Tomography scan in staging and specifically in the diagnosis of bone marrow involvement has also been suggested [10]. The International Prognostic Index is calculated using the patient's age, Ann Arbor stage, number of extranodal sites involved, performance status and serum LDH. This predicts survival and risk of recurrence with statistical significance [11]. The classification of NHL has evolved over time, from the International Working Formulation (IWF) criteria in 1981, including the Rappaport and Kiel systems, to the WHO/Revised European American Lymphoma classification (REAL), in 1994 [12]. Further updates incorporating immunophenotypes have taken place along with the WHO 2008 review. Therefore direct comparison between the different classification systems is not always possible.

In the reported cases, therapeutic approach ranged from surgery with adjuvant radiotherapy for localised disease along adjuvant chemotherapy for advanced disease, to chemotherapy alone. Over the last few years, immuno-chemotherapy regimens have established efficacy and recently immune-therapy alone and conservative approach for asymptomatic early stages is taking place. The therapeutic value of surgery seems to be limited besides providing histological diagnosis. Indolent NHL is extremely responsive to immunotherapy, which also has the benefit of preserving fertility. Successful pregnancies have been reported following treatment, but early involvement of a fertility specialist for consideration of egg or embryo freezing is recommended [13, 14].

The therapeutic approach to the rare isolated genital tract NHL is not standardised and management is influenced by the general principals of NHL treatment. Non aggressive asymptomatic NHL can be managed with watchful waiting or radiotherapy in the case of nodal involvement. Current guidelines for management of symptomatic patients with stage III and IV follicular NHL suggest rituximab based regimes. It is used alone or in combination with conventional chemotherapy regimes, such as cyclophosphamide, vincristine and prednisolone (CVP), cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), mitoxantrone, chlorambucil and prednisolone (MCP) cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α (CHVPi), chlorambucil, and recently bendamustine [15]. Rituximab is recommended as a maintenance therapy for patients with follicular NHL which have responded to first-line induction therapy with rituximab in along with chemotherapy [16]. Rituximab alone or in combination with chemotherapy is recommended for patients with relapsed stage III or IV follicular NHL whose previous remission was induced with chemotherapy with or without rituximab. Rituximab is also recommended for patients with relapsed or refractory disease when all alternative treatment options have been exhausted [17]. Autologous stem cell transplantation consistently improves progression free survival and event-free survival (EFS) in follicular NHL, but comparative data with rituximab-containing regimens are lacking. Moreover due to higher incidence of secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), it is not recommended as first-line treatment [18].

For aggressive localised NHL the addition of radiotherapy post chemotherapy does not seem to offer any benefit in progression free or overall survival [19]. The addition of rituximab to the CHOP chemotherapy, for initial and recurrence treatment of aggressive NHL has improved overall survival for DCBL. While

R-CHOP is used for primary treatment, many combinations have been used for recurrent disease, in addition to the recently added rituximab monotherapy. Management for the less common forms of aggressive NHL (MCL and PTCL), is less unified amongst experts and cure rates are significantly lower [20]. Autologous stem cell transplantation could be considered for recurrent or refractory DCBL with complete or partial remission, but its use as a first line treatment in aggressive NHL is not supported by a recent metanalysis [20, 21].

Due to rarity of genital tract isolated extranodal NHL management approach varies and seems to be individualised. Prognosis appears to be worse in advanced stage disease, but its relation with the different histological types is not completely clear. The use of multimodal treatments, the fact that surgery frequently takes place before diagnosis, and the differences in histological classification——obscure the benefit of each therapeutic modality. The role of surgery appears to be limited, while that of immunotherapy and chemotherapy significant.

Abbreviations

NHL, non-Hodgkin Lymphoma; DLBCL, diffuse large B-cell lymphoma; PTCL, peripheral T-cell lymphoma; MCL, mantle cell lymphoma; LLETZ, large loop excision of transformation zone; CIN, cervical intraepithelial neoplasia; CD, cluster of differentiation; BCL, B-cell lymphoma; CKAE, Cyto Keratine Antibodies; EUA, examination under anaesthesia; LDH, lactated dehydrogenase; FIGO, International Federation of Gynecology and Obstetrics; IWF, International Working Formulation; REAL, WHO/Revised European American Lymphoma classification; WHO, World Health Organisation; CVP, cyclophosphamide, vincristine, prednisolone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone MCP, mitoxantrone, chlorambucil, prednisolone; CHVPi, cyclophosphamide, doxorubicin, etoposide, prednisolone, interferon-α; EFS, event-free survival; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia.

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