Primary Diffuse Large B-Cell Lymphoma of the Uterus: Case Report and Review

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Abstract. *Background: Primary diffuse large B-cell lymphoma of the cervix is a very rare disease, with non-specific clinical presentation. Its prognosis depends on accurate and timely diagnosis and therapy. Moreover, the management of this tumour has never been standardized. Case Report: Herein we present a rare case of primary diffuse large B-cell lymphoma of the cervix misdiagnosed as cervical myoma. Our systematic review of the English literature identified 143 cases of primary diffuse large B-cell lymphoma of the uterus. Patients' characteristics and oncological, surgical, and safety data were recorded and analyzed. Conclusion: Although rare, primary diffuse large B-cell lymphoma of the cervix should never be ruled-out. Given its non-specific clinical symptoms, a multidisciplinary approach is required to perform a timely diagnosis and administer appropriate therapy. Immunochemotherapy (Rituximab + CHOP or CHOP-like regimen) with/without radiotherapy is the most common and most effective treatment; surgery should be avoided.*

The incidence rate of non-Hodgkin's lymphoma (NHL) is approximately 20 per 100,000 population (1), with the primary site usually in the lymph nodes and other lymphoid tissues such as the spleen and bone marrow. However, in approximately one-third of patients, NHL affects the extranodal regions (2), including the female genital tract, with an incidence rate ranging from 0.5 and 1.5% (3, 4). NHL can occur in the ovary, *corpus uteri* (CO), *cervix*, vagina, or vulva; the most frequent site in the gynaecological tract is under debate, although most authors consider it to be the ovary (4). Primary malignant lymphoma of the cervix is a very rare disease, representing only 0.008% of all cervical tumors and 2% of all female extranodal lymphomas (5, 6). Clinical symptoms are usually non-specific and include vaginal bleeding (70%), perineal discomfort (40%), and persistent vaginal discharge (20%) (7). While the most common histological type is diffuse large B-cell lymphoma (DLBCL) (4, 8), patients may lack the "B" symptoms often associated with lymphoma, *i.e.* fever, weight loss, night sweats, and fatigue. Because of the rarity of this tumor and the non-specific symptoms, diagnosis, staging, and therapy of cervical DLBCL are often difficult and delayed. Moreover, the management of this disease has never been standardized (1-94).

The aims of the current study were to describe a case of primary aggressive B-cell lymphoma of the cervix which was diagnosed and treated at our public Hospital using a multi-disciplinary approach and to systematically review the English literature in order to identify the most common clinical presentation, methods of diagnosis, treatment approaches, and prognosis of primary aggressive B-cell non-Hodgkin's lymphoma of the uterus.

Case Report

A 44-year-old woman was referred to the Unit of Obstetrics and Gynecology with vaginal bleeding. The patient was negative for fever, weight loss, nausea, vomiting, and night sweats, and the Papanicolaou (PAP) smear was negative. The patient underwent diagnostic hysteroscopy followed by endometrial sampling: no visible lesions were detected and biopsies were negative. At transvaginal ultrasound examination, an abnormal mass resembling a myoma (5×3 cm) was observed between the cervix and bladder (Figure 1). One month later, the patient experienced persistent vaginal bleeding. At follow-up visit, the mass had not increased in

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Key Words: Uterus, cervix, diagnosis, lymphoma, treatment, vaginal bleeding.

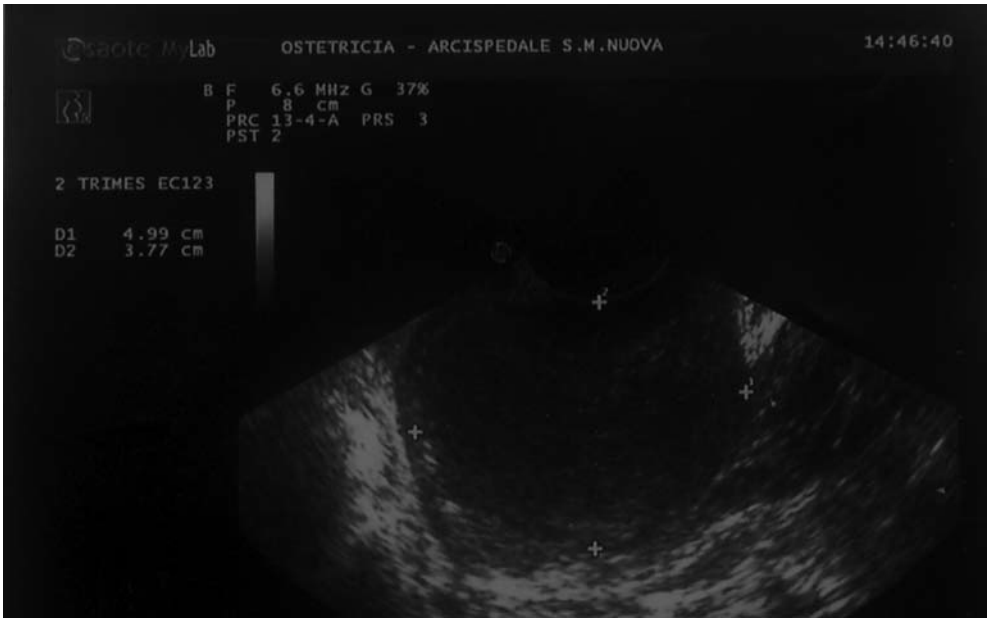

Figure 1. *Ultrasound appearance of diffuse large B-cell extranodal lymphoma of the cervix misdiagnosed as a myoma.*

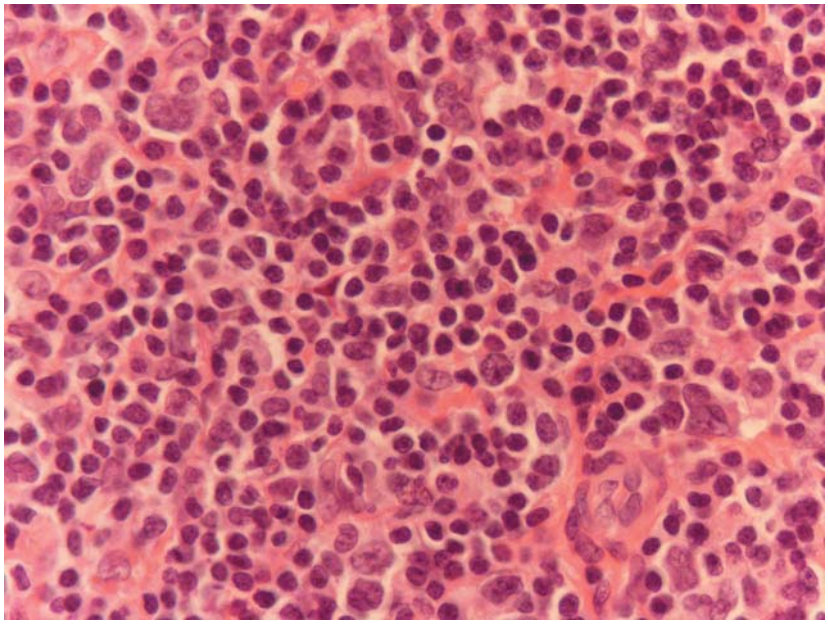

Figure 2. *Haematoxylin-eosin staining showing a diffuse proliferation of medium- vs large-sized lymphoid cells. Original magnification, ×200.*

size. Based on the above-described scenario, we suspected a uterine myoma and thus recommended a vaginal myomectomy. The intraoperative finding was a necrotic cerebroid tissue, which was sent for intraoperative analysis by frozen section. Microscopic examination of frozen sections raised three diagnostic options: small-cell neuroendocrine carcinoma, extranodal NHL, or undifferentiated cervical carcinoma. Considering the patient's age and that radical vaginal excision was impossible due to the extension of the tumor, a laparotomic class-B radical hysterectomy was performed. The macroscopic examination revealed a grey mass measuring 5 cm in maximum size of the cervicovaginal

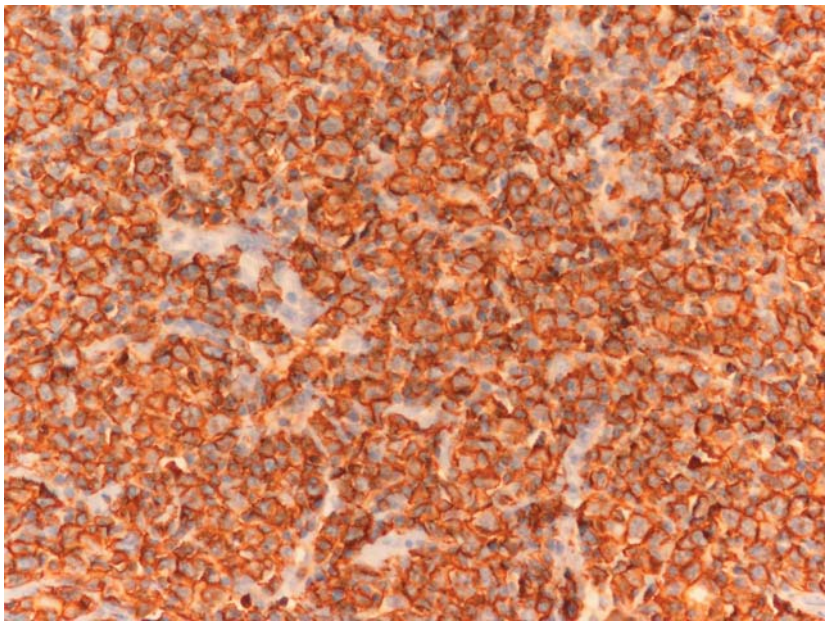

Figure 3. *Immunohistochemically, these elements were positive by Cluster of Differentiation 20 stain, supporting a B phenotype. Original magnification, ×200.*

area without endometrial involvement. Microscopic examination revealed proliferation of large atypical lymphoid cells (Figure 2). Immunohistochemically, these elements were cluster of differentiation (CD) 20-positive B lymphocytes (Figure 3) and the proliferative fraction as detected by Ki-67 staining was high (Figure 4).

A diagnosis of diffuse large B-cell extranodal lymphoma (DLBCL) was rendered. An enlarged external right iliac lymph node was negative for lymphomatous infiltration. In light of the histological diagnosis, the patient was referred to the haematologist.

To perform a complete, accurate, and definitive staging of the disease, the patient underwent positron-emission tomography (PET), total-body computed tomography (CT), bone marrow biopsy, haematochemical examinations, echocardiographic and cardiologic assessments, and, finally, spirometry. PET scan was positive for a right iliac lymph node. CT scan was negative for adenopathy and/or organomegalies. Haematochemical tests showed no abnormal results except for erythrocyte sedimentation rate (44 mm), alkaline phosphatase (602 U/l), gamma glutamyl-transpeptidase (167 U/l), glutamic oxaloacetic transaminase and glutamic-pyruvic transaminase (33/94 U/l). Echocardiogram, bone marrow biopsy, and spirometry were all negative. Due to the extensive involvement of the cervix and the upper zone of the vagina, the patient was classified as having a stage IVEA disease according to the Ann Arbor staging system (95). The age-adjusted International Prognostic Index was 1 (stage IV). The patient was informed of, and gave her written consent to enter the Unfolder randomised study comparing an

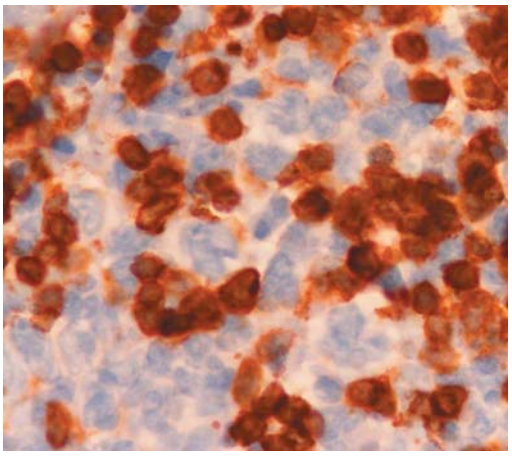

Figure 4. *The proliferative fraction as detected by Ki67 staining is high. Immunohistochemical stain for Ki67, magnification ×400.*

immunochemotherapy with six cycles of the monoclonal antibody against CD20 (rituximab) in combination with six cycles of chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (CHOP) at 21-day intervals or 14-day intervals, both with or without consolidating radiotherapy of large tumour masses (≥7.5 cm) and/or extranodal involvement in patients with aggressive CD20-positive B-cell lymphoma aged 18 to 60 years with age-adjusted IPI=1 (all) or IPI=0 with bulky disease (≥7.5 cm). She was randomized to receive six courses of CHOP therapy associated with rituximab every 21

Table I. *Outcomes of case reports of aggressive B-cell primary cervical and corpus uteri non-Hodgkin's lymphoma categorized by treatment.*

Reference	Age (years)	Clinical presentation	Site	Diagnosis	Sub-type*	Stage	Treatment (months)	Outcome
XRT alone								
Sobotkowski *et al*. 2004 (78)	77	Vaginal bleeding	CE	NR	DLBCL	IEA	XRT	CR at 48
Muntz *et al*. 1991 (64)	73	Vaginal bleeding	CE	Biopsy	Diffuse large cell	IEA (4 cm)	XRT (40 Gy)	CR at 60
Muntz *et al*. 1991 (64)	23	Abdominal pain, Vaginal bleeding	CE	Biopsy	Diffuse large cell	IEA (5 cm)	Ovarian transposition/XRT	CR at 54
Amichetti *et al*. 1999 (24)	82	Vaginal bleeding	CE	Biopsy	IWF: H	IEA	XRT (65Gy)	CR at 6
Awwad *et al*. 1994 (27)	27	Vaginal bleeding	CE	Biopsy	IWF: I	IE (7cm)	XRT (92 Gy)	DWD at 7
Perren *et al*. 1992 (71)	54	Vaginal bleeding	CE	Biopsy	Diffuse large cell	IIEA (5cm)	XRT (40 Gy)	CR at 240
Maryniak *et al*. 1993 (62)	53	Pelvic discomfort	CE	Laparotomy	DLBCL	IIE	XRT (3000 cGy)	DWD at 38
CT alone								
Amichetti *et al*. 1999 (24)	81	Vaginal bleeding	CE	Biopsy	Lymphoblastic lymphoma	IEA (10 cm)	PEN×6	AWD at 14
Nasu *et al*. 1998 (65)	64	Vaginal discharge	CE	Biopsy	DLBCL	IEA (10 cm)	THP-COP×10	CR at 18
Stroh *et al*. 1995 (19)	64	Vaginal bleeding	CE	Biopsy	DLCL	IEA	CHOP-B	DWD at 11
Au *et al*. 2003 (26)	45	Vaginal discharge	CE	Biopsy	DLBCL	IIEA (10 cm)	m-BACOD	CR at 10
Perren *et al*. 1992 (71)	47	Vaginal bleeding	CE	Biopsy	IWF: F	IIEB	CHOP×6	CR at 60
Samama *et al*. 2011 (74)	79	Urinary obstruction	CO	Laparotomy	DLBCL	IVA	R-CHOPx6	DWD at 9
Upanal *et al*. 2011 (83)	49	Gastrointestinal symptoms, vaginal discharge	CE	Cervical biopsy	DLBCL	IEA (8 cm)	R-CHOP×6	CR at 20
Rajnics *et al*. 2009 (94)	45	Vaginal bleeding	CO	Abdomen/ pelvic CT scan punch biopsy	DLBCL	IE	R-CHOP×6	CR at 40
Rajnics *et al*. 2009 (94)	26	Vaginal bleeding	CO	Endometrial curettage	DLBCL (8cm)	IE	R-CHOP×6	CR at 60
Dursun *et al*.. 2005 (36)	49	Routine exam follow-up	CE	Pap smear/ Cervical biopsy LEEP	FL GR III	IE	CHOP×6	CR at 22
Hanprasertpong *et al*. 2008 (92)	25	Postcoital bleeding and increasing vaginal discharge	CE	Cervical biopsy	DLBCL (5.7cm)	IE	CHOP×6	CR at 29
Cohn *et al*. 2007 (3)	46	Abdominal fullness, vaginal bleeding, discharge	CE	Pelvic CT scan +vaginal biopsy	DLBCL	IV (4 cm)	R-CHOP×6	DWD at 18
Ab Hamid and Wastie 2008 (6)	43	Postcoital bleeding	CE	Cervical biopsy	DLBCL (8 cm)	IE	CHOP×6	NR
Renno *et al*. 2002 (73)	69	Vaginal bleeding	CO	Pelvic ultrasonography	DLBCL	IV	CT	CR at 21
Pham *et al*. 2003 (72)	36	Abnormal cervical cytology	CE	Biopsy	DLBCL	I – EB	CHOP×6 + Antiretroviral therapy	CR at 38
Thyagarajan *et al*. 2004 (81)	41	Vaginal bleeding, urinary symptoms	CE	MRI	DLBCL	IV (12 cm)	CHT×8 + XRT	CR at 7
Sandvei *et al*. 1990 (75)	22	Spotting, postcoital bleeding	CE	Cervical biopsy	NHL	IE-A (3 cm)	CHOP x 6	CR at 72
Al - Talib *et al*. 1996 (22)	45	Postcoital bleeding	CE	Colposcopy	DLBCL	IEA	CT	CR at 24
Al - Talib *et al*. 1996 (22)	20	No symptoms	CE	Cervical smear	DLBCL	IEA	CT	CR at 9
Kim *et al*. 1997 (47)	60	Lower abdominal mass, chilling	CO	MRI	DLCNHL	N.R.	CT	NR
Clarke *et al*. 1998 (34)	28	Postcoital bleeding	CE	Rectovaginal examination	HGBCNHL	I EA	CHOP	CR at 6
Malatskey *et al*. 1991 (59)	45	Vaginal bleeding	CE	Ultrasonographic examination	DLBCL	IVE (8 cm)	CHOP	NR
Kawakami *et al*. 1995 (46)	60	Lower abdominal mass	CO	MRI	Medium and large B cell	IVE A	CT	NR
Venizelos *et al*. 1993 (87)	33	Vaginal bleeding	CE	Cervical -biopsy	DLBCL	II A	CHOP	CR at 10
Bilgin *et al*. 1999 (28)	74	Vaginal bleeding	CE	Cervical biopsy	D Small – CL	III E	CHOP × 6	CR at 24
Van Renterghem *et al*. 2005 (86)	45	Vaginal discharge	CE	Cervical polipectomy	DLBCL	I EA	ACVBP ×3 + VIA-MTX subcutaneously	CR at 18

Table I. *Continued*

Table I. *Continued*

Reference	Age (years)	Clinical presentation	Site	Diagnosis	Sub-type*	Stage	Treatment (months)	Outcome
Broekmans *et al*. 1993 (30)	45	Slight postcoital bleeding	CE	Cervical polypectomy	DLBC	IE	CHOP - MTX×6	CR at 36
Aozasa *et al*. 1993 (25)	78	Lumbago	CO	Biopsy	DLBC	III	Prednisolone	DWD at 1
Hariprasad *et al*. 2006 (41)	80	Vaginal bleeding, anorexia, mass in vagina	CE	Cervical biopsy	DLBCL	IE	CHOP×6	CR at 4
Chan *et al*. 2005 (32)	41	Severe weakness, abdominal pain, weight loss, night sweats	CE	Laparotomy	DLBCL	IIIEB (6 cm)	CHOP×8	CR at 40
Chan *et al*. 2005 (32)	52	Vaginal bleeding, weight loss, fatigue	CE	Cervical biopsy	Predominantly large B cell lymphoma	IVEB (14 cm)	R-CHOPx8	CR at 12
Groszmann and Benacerraf 2013 (39)	25	Vaginal bleeding	CE	Sonography	LBCL		CT	CR at 12
Surgery alone								
Vang *et al*. 2000 (9)	35	Vaginal bleeding	CO	Not specified	DLBCL	IEA	TAH	NR
Vang *et al*. 2000 (9)	46	Abdominal pain	CE	Cervical biopsy	DLBCL	IEA	TAH + BSO	CR at 54
Lemos *et al*. 2008 (55)	89	Vaginal bleeding	CO	Hysteroscopy	DLBCL	IVE	TAH + BSO	DWD at 5
Iyengar and Deodhare 2003 (44)	65	Vaginal bleeding	CO	Hysteroscopy	MALT	IE	TAH +BSO	NR
Frey *et al*. 2006 (11)	43	Vaginal bleeding	CO	Endometrial biopsy	EMZL	IIE	TAH+BSO+ sampling	CR at 28
Heeren et al 2008 (93)	61	Vaginal prolapse	CO	Vaginal hysterectomy	EMZL	IE	Total surgical resection	CR at 8
Dhimes *et al*. 1996 (35)	69	Incidental	CE	Cervical biopsy	Small diffuse B cell NHL	IE (6 cm)	TAH	CR at 12
Olde Scholtenhuis *et al*. 2002 (76)	78	Vaginal bleeding	CO	Hysteroscopy	DLBCL	IE	TAH	CR at 168
Aozasa *et al*. 1993 (25)	46	Abdominal pain, weight loss	CO	Not specified	DIB	II	Probe laparotomy	DWD at 3
Surgery + XRT								
Lee *et al*. 1998 (53)	67	Vaginal bleeding	CE	Cervical polypectomy	DLBCL	IEA	TAH + BSO + WRT (46 Gy)	CR at 120
Lee *et al*. 1998 (53)	65	Vaginal bleeding	CE	Cervical biopsy	DLBCL	IEA	TAH+BSO + WRT (40 Gy)	CR at 120
Muntz *et al*. 1991 (64)	73	Vaginal bleeding	CE	Cervical biopsy	IWF: I	IEA	TAH +BSO + XRT	CR at 54
Muntz *et al*. 1991 (64)	30	Vaginal bleeding	CE	Cervical biopsy	IWF: I	IEA (4 cm)	TAH +BSO/ XRT (40 Gy)	CR at 120
Maryniak and Nasierowska-Guttmejer. 1993 (62)	72	Vaginal bleeding, thickening, submucosal infiltration	CE	Hysterectomy	DLBCL	IE	TAH + XRT (3960 cGy)	DWD at 18
Papadopoulos *et al*. 1996 (67)	36	Vaginal and postcoital bleeding	CE	Hysterectomy	DLBCL	IEB (9 cm)	TAH + CHOP×8	CR at 48
Maryniak and Nasierowska-Guttmejer. 1993 (62)	24	Vaginal bleeding, thick infiltration	CE	Hysterectomy	LGBCL	II E	TAH + XRT (3960 cGy)	NR
Aozasa *et al*. 1993 (25)	30	Vaginal bleeding	CE	Hysterectomy	DLCL	II	TAH + XRT (Gy 39.6)	DWD at 20
Aozasa *et al*. 1993 (25)	41	Vaginal bleeding	CE	Hysterectomy	DLCL	II	TAH + BSO + XRT (Gy 30)	DWD at 8
Aozasa *et al*. 1993 (25)	71	Vaginal bleeding	CE	Biopsy	Diffuse lymphoma	I	Resection + XRT (Gy 36)	DWD at 24
Chan *et al*. 2005 (32)	76	Vaginal discharge	CE	CT scan	Intermediate large cell diffuse	IEA (3 cm)	TAH + BSO + LMP + XRT	CR at 14

Table I. *Continued*

Table I. *Continued*

Reference	Age (years)	Clinical presentation	Site	Diagnosis	Sub-type*	Stage	Treatment (months)	Outcome
Surgery+CT								
Cahill *et al*. 1997 (31)	31	Vaginal bleeding	CO	Biopsy	DLBCL	IEA (3.5 cm)	TAH + BSO+ CT	CR at 48
Dursun *et al*. 2005 (36)	51	Vaginal discharge	CE	Colposcopy	DLBCL	IEA	TAH+ BSO + CHOP×6	CR at 19
Makarewicz and Kuzminska 1995 (58)	33	Vaginal discharge	CE	NR	Kiel: centroblastic	IEA	TAH+BSO + CHOP×6	CR at 42
Gabriele and Gaudiano 2003 (37)	40	Vaginal bleeding	CE	Hysterectomy	IWF: I	IEA (6 cm)	TAH + CHOP×6	CR at 27
Szánthó *et al*. 2003 (80)	56	Vaginal bleeding	CE	Cervical biopsy	DLBCL	IEA (8 cm)	TAH + BSO/ CHOP×6	CR at 60
Wang *et al*. 1999 (88)	35	Obstruction of labour	CE	Hysterectomy	IWF: I	IEA	TAH+BSO + mBACOD×4	CR at 28
Grace *et al*. 1999 (38)	35	Vaginal bleeding	CE	Cervical biopsy	DLBCL	IEA	TAH + CHOP×4	NR
Yamada *et al*. 2005 (89)	42	S/P TAH for leiomyomata	CO	Hysterectomy	DLBCL (intravasc sub-type)	IEA	TAH+ R-CHOP×6	CR at 10
Vang *et al*. 2000 (9)	67	Routine exam	CE	Cervical biopsy	DLBCL	IEA	Conization +CT	CR at 108
Garavaglia *et al*. 2005 (7)	35	Vaginal bleeding, enlarged cervical lesion of 5 cm	CE	Biopsy	DLBCL	IIEA (5 cm)	TAH+ CHOP×4	CR at 72
Garavaglia *et al*. 2005 (7)	38	Irregular nodular lesion of vagina	CE	Biopsy	DLBCL	IE	TAH + MACOP-B×12	CR at 10
Garavaglia *et al*. 2005 (7)	38	Enlarged eroded cervical lesion of 5 cm and vaginal nodule	CE	Biopsy	DLBCL	IIE (5 cm)	TAH + MACOP-B×12	CR at 84
Tan *et al*. 2011 (8)	43	Routine ultrasound	CO	Biopsy	Precursor B cell Lym Lymph	IE (5 cm)	TAH+SOB+ LMP+R-CHOP +Arab	CR at 42
Hatami *et al*. 2010 (42)	58	Routine ultrasound	CO	Laparotomy	Burkitt	IVA (15×10 cm)	R- VCR+MTX +Leucovorin	CR at 41
Hanley *et al*. 2009 (40)	52	Vaginal bleeding	CO	Abdominal ultrasound Liquid based Pap smear	DLBCL	IV (20 cm)	TAH+SOB+ Staging+ VAC	AWD at 4
Frey *et al*. 2006 (11)	35	Vaginal bleeding	CE	Biopsy	DLBCL	IIE (9 cm)	TAH+ R -CHOP×4	CR at 36
Frey *et al*. 2006 (11)	56	Vaginal bleeding	CO	Vaginal ultrasound	DLBCL	IIE (15 cm)	TAH+BSO+R-CHOP ×8	CR at 6
Frey *et al*. 2006 (11)	49	Vaginal bleeding	CE	Vaginal ultrasound	DLBCL	IIE (8 cm)	TAH+BSO+R-CHOP ×6 +R×4	CR at 32
Tan *et al*. 2011 (8)	43	Intrauterine mass	CO	Pelvic ultrasound	Precursor B cell Lym Lymph	IIE (5 cm)	TAH+BSO+ SAMPLING+ R-CHOP ×6	CR at 42
Su *et al*. 2008 (14)	69	Vaginal bleeding	CO	Endometrial sampling	DLBCL	IV	TAH+BSO+R-CVP ×8	CR at 36
Semczuk *et al*. 2006 (77)	43	Pap test	CE	Ultrasound	DLBCL	IE (10 cm)	TAH+CHOP ×6	CR at 10
Pasini *et al*. 1991 (69)	35	Postcoital bleeding	CE	Ultrasound	NHL	IIE (3 cm)	TAH+BSO+ CHOP ×6	CR at 12
Kuo *et al*. 1994 (51)	40	Vaginal discharge	CE	Cervical biopsy	DLBCL	IEA (6 cm)	RH +BSO+ COP – BLAM ×6	CR at 24
Marin *et al*. 2002 (61)	63	Asymptomatic	CE	TAH	Lymphoblastic lymphoma	IEA	TAH +CHOP	NR
Alvarez *et al*. 1997 (23)	78	Vaginal bleeding	CO	Endometrial cutterage	DLBCL	I (7 cm)	TAH/BSO + CHOP×6	CR at 84
Ohwada *et al*. 2000 (66)	59	Vaginal bleeding	CO	Endometrial cytology	DLBCL	IE (5 cm)	TAH+BSO+ CT ×6	CR at 10
Abbas *et al*. 1996 (21)	25	Vaginal bleeding	CE	Biopsy	DLBCL	IEA (8 cm)	Surgical resection + CT	CR at 2
Kawakami *et al*. 1995 (46)	66	Lower abdominal mass	CE	Laparotomy	DLBCL	IEA	Surgery + CT	NR
Aozasa *et al*. 1993 (25)	64	Vaginal bleeding	CO	Total hysterectomy	DIB	I	TAH + BSO + CHOP	DWD at 12

Table I. *Continued*

Table I. *Continued*

Reference	Age (years)	Clinical presentation	Site	Diagnosis	Sub-type*	Stage	Treatment (months)	Outcome
Chan *et al*. 2005 (32)	62	Vaginal discharge, pelvic pain	CE	Trachelectomy	High grade small cell non Burkitt	IEA (6 cm)	Trachelectomy+ BACOD×6	CR at 72
Chan *et al*. 2005 (32)	49	Vaginal bleeding, abdominal pain	CE	Cervical biopsy	High grade lymphoblastic	IVEB (6 cm)	TAH + R-CHOP ×8	CR at 36
Current Study	44	Vaginal bleeding	CE	Radical abdominal hysterectomy	DLBCL	IVEA (4 cm)	RH +R-CHOP×6	CR at 24
XRT+CT								
Mansouri *et al*. 2001 (60)	34	Vaginal bleeding	CE	Cervical biopsy	IWF: I	IEA (bulky)	CHOP×6/ XRT (46 Gy)	CR at 48
Kostopoulos *et al*. 2000 (50)	64	S/P TAH for leiomyoma	CE	TAH+BSO	DLBCL	IEA	Unavailable	NR
Amichetti *et al*. 1999 (24)	67	Vaginal bleeding	CE	Cervical biopsy	IWF: I	IEA	CHOP×6/XRT (40 Gy)	CR at 106
Amichetti *et al*. 1999 (24)	60	Urinary frequency	CE	Cervical biopsy	IWF: I	IEA	CHOP×6/XRT (44.6 Gy)	CR at 122
Amichetti *et al*. 1999 (24)	37	Vaginal bleeding	CE	Cervical biopsy	IWF: I	IEA	CHOP×4/XRT (40 Gy)	CR at 126
Chandy *et al*. 1998 (33)	50	Vaginal bleeding	CE	Cervical biopsy	DLBC	IEA (10 cm)	CHOP×4/XRT (46 Gy)/CHOP×2	CR at 24
Makarewicz and Kuzminska 1995 (58)	37	Vaginal bleeding	CE	Cervical biopsy	Kiel: centroblastic	IEA	CVP×3/XRT (45 Gy)	CR at 96
Makarewicz and Kuzminska 1995 (58)	65	Vaginal bleeding	CE	Cervical biopsy	Kiel: lymphoblastic	IEA	CHOP×6/XRT (44 Gy)	CR at 36
Stroh *et al*. 1995 (19)	53	Pelvic pain	CE	Biopsy of pelvic mass	IWF: I	IEA (10 cm)	CHOP-B/XRT (40 Gy) /CHOP-B	CR at 173
Stroh *et al*. 1995 (19)	64	Vaginal bleeding	CE	Biopsy of pelvic mass	IWF: I	IEA (8 cm)	CHOP-B/XRT (90 Gy)	CR at 165
Stroh *et al*. 1995 (19)	67	Vaginal bleeding	CE	Biopsy of pelvic mass	IWF: I	IEA	ASHAP/MBACOS/ MINE/XRT (40Gy)	CR at 18
Stroh *et al*. 1995 (19)	66	Routine exam	CE	Biopsy of pelvic mass	IWF: I	IEA (3 cm)	CHOP/XRT (40 Gy)	CR at 37
Vang *et al*. 2000 (9)	39	Routine exam	CE	Cervical biopsy	DLBCL	IEA	CHEMO/XRT	CR at 7
Heredia *et al*. 2005 (12)	32	Vaginal bleeding	CE	Cervical biopsy	DLBCL	IEA (8 cm)	CHOP×3/XRT (45 Gy)	CR at 61
Yokoyama *et al*. 2001 (90)	55	Vaginal discharge	CE	Cervical biopsy	DLBCL	IEA (8 cm)	CEOP×3/XRT (50 Gy)	CR at 12
Stroh *et al*. 1995 (19)	39	Abdominal pain	CE	biopsy of pelvic mass	IWF: I	IEA (4 cm)	XRT (48 Gy)/ CHOP-B	CR at 142
Upanal and Enjeti 2011 (83)	51	Abdominal pain, dyspareunia	CE	Large loop excision of transformation zone procedure	DLBCL	IIEA (9cm)	R-CHOP×6 ERT (30 Gy)	CR at 19
Ustaalioglu *et al*. 2010 (84)	65	Vaginal bleeding, fever, weight loss	CE	Cervical biopsy	DLBCL	IEB (9 cm)	R-CHOP×6 / ERT (36 Gy)	CR at 10
Kendrick and Straughn 2005 (20)	47	Vaginal discharge, ulcerated cervical lesion extending to the upper vagina	CE	Biopsy	DLBCL	IEA	R-CHOP×4	CR at 6
Stroh *et al*. 1995 (19)	57	Vaginal bleeding	CO	N.R.	IWF: I	IIEA	CHOP-B/CMED/ XRT (40 Gy)	CR at 67
Stroh *et al*. 1995 (19)	49	Routine exam	CE	N.R.	IWF: I	IIEA	ASAP/BACOS/ MINE/XRT (40.8 Gy)	CR at 37
Vang *et al*. 2000 (9)	57	Vaginal bleeding	CE	Cervical biopsy	DLBCL	IIEA	CHEMO/XRT	CR at 60
Heredia *et al*. 2005 (12)	31	Vaginal bleeding	CE	Cervical biopsy	DLBCL	IIEA (9 cm)	mCHOP×4/ XRT (36 Gy) TAH	CR at 15
Novotny *et al*. 2011 (10)	82	Fever, abdominal pain, altered mental status, bilateral hydronephrosis	CE	Cervical biopsy	DLBCL	IVB	Palliative therapy	DWD at 2 weeks

Table I. *Continued*

Table I. *Continued*

Reference	Age (years)	Clinical presentation	Site	Diagnosis	Sub-type*	Stage	Treatment (months)	Outcome
Cohn *et al*. 2007 (3)	22	Pelvic pressure, dysmenorrhea, vaginal bleeding	CE	Cervical biopsy	DLBCL	IE (4 cm)	R-CHOP×6 + XRT	NR
Cantù de Leòn *et al*. 2006 (5)	56	Lower abdominal pain, arthralgia, vaginal bleeding	CE	Colposcopy	DLBCL	IIE	CHOP×8 + XRT	CR at 6
Korcum *et al*. 2007 (4)	67	Vaginal bleeding, back pain	CE	Cervical biopsy	LGFNHL	IEA	CHOP×3 + ERT	CR at 39
Trenhaile and Killackey 2001 (82)	66	Vaginal bleeding, abdominal distension	CO	Biopsy	DLBCL	IIE	CHOP×6 + XRT	CR at 25
Kahlifa *et al*. 2003 (45)	32	Vaginal bleeding, lower abdominal pain, weight loss	CE	Parametrial biopsy + curettage	DLBCL	IEA (11cm)	CHOP×6 + XRT (3000 cGY)	CR at 10
Liang *et al*. 1990 (56)	76	NR	CE	NR	diffuse immunoblastic B-cell lymphoma	I	COPP + RT	CR at 45
Bortolus *et al*. 1997 (29)	65	Vaginal bleeding	CE	Biopsy	DLBCL	I EA	CHVmP/BV + RT (45 Gy)	CR at 77
Bortolus *et al*. 1997 (29)	55	Vaginal bleeding	CE	Endometrial biopsy	DLBCL	II EA	CHVmP/BV + RT (45 Gy)	CR at 66
Van Renterghem *et al*. 2005 (86)	38	Vaginal bleeding, lower abdominal pain, lumbalgia	CE	Cervical biopsy	DLBCL	II E	CEOP×3/ XRT (28 Gy)	CR at 48
Kawakami *et al*. 1995 (46)	63	Vaginal bleeding	CE	MRI	Small B cell NHL	IVA	CT + RT	NR
Binesh *et al*. 2012 (91)	85	Vaginal bleeding	CE	Cervical biopsy	DLBCL	IE	ONCOVIN+ Prednisone + RT	CR at 5
Lien 1994 (57)	70	NR	CO	MRI	NHL	IEA	CT + RT	CR at 48
Olde Scholtenhuis *et al*. 2002 (76)	79	Vaginal bleeding	CO	Vaginal inspection	DLBCL	IIIE	CHOP + RT	CR at 32
Aozasa *et al*. 1993 (25)	71	Vaginal bleeding	CE	Autopsy	DLBCL	N.R.	Mitomycin C (peritoneal injection) + RT (1.5 Gy)	DWD at 2
Hariprasad *et al*. 2006 (41)	47	Vaginal bleeding	CE	Cervical biopsy	DLBCL	IE	CHOP×3 +CVP ×3 + RT (45 Gy)	CR at 4
Chan *et al*. 2005 (32)	40	Vaginal bleeding, abdominal pain	CE	Cervical biopsy	IWF: interme-diate, DLBCL	IVEA (12 cm)	CHOP ×8 + RT	CR at 120
Parnis *et al*. 2012 (68)	54	Vaginal bleeding	CE	Cervical biopsy	DLBCL	IE	R-CHOP×6 + RT (3Gy5)	CR at 17
Baijal *et al*. 2009 (2)	44	Vaginal bleeding	CE	Biopsy	DLBCL	IE (7 cm)	R-CHOP×3 + RT (Gy46)	CR at 15
Isosaka *et al*. 2013 (43)	67	Vaginal bleeding	CO	Biopsy	DLBCL	IE	R-CHOP×6 + RT	CR at 24
Surgery+XRT+CT								
Latteri *et al*. 1995 (52)	46	Vaginal bleeding	CO	TAH+BSO	NHL	IEA	TAH + RT (45 gray) + ProMACEMOPP×8	CR at 30
Patsner and Greenberg 1995 (70)	38	Vaginal bleeding	CE	Pelvic ultrasound	NHL	I E	RH (emergency) + CHOP ×6 + RT (5000 cGy)	CR at 36
Treatment not reported								
Kim *et al*. 1997 (47)	24	Vaginal bleeding	CE	MRI	DLCL	NR	NR	NR
Kim *et al*. 1997 (47)	53	Vaginal bleeding	CE	Laparotomy	DLCL	NR	NR	NR
Mehta and Thurston 1998 (63)	24	Urinary retention	CE	MRI	B-cell NHL	IEA	NR	NR
Mehta and Thurston 1998 (63)	68	Vaginal bleeding	CE	MRI	B-cell NHL	IEA	NR	NR
Koliopoulos *et al*. 2000 (50)	59	Vaginal bleeding	CO	Laparotomy	Precursor B cell lymphoblastic lymphoma	IV	No treatment	DWD at 3 days
Suzuki *et al*. 2000 (79)	66	Lumbago, appetite loss	CO	Autopsy	DLBCL	IVA	No treatment	DWD at 2
Van de Rijn *et al*. 1997 (85)	66	Asymptomatic	CO	Curettage specimen	DLBCL	IEA	TAH+LMP	NR
Van de Rijn *et al*. 1997 (85)	68	Asymptomatic	CO	Hysterectomy	DLBCL	IEA	TAH	NR

ACVB: Bleomycin, cyclophosphamide, doxorubicin, vincristine; BSO: Bilateral salpingo-oophorectomy; CE: cervix; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CHOPE: cyclophosphamide, doxorubicin, vincristine, prednisone and etoposide; CO: corpus; CR: cure rate; CT: chemotherapy; CVP: cyclophosphamide, vincristine and prednisone; DIB: diffuse immunoblastic; DLBCL: diffuse large B cell lymphoma; DWD: died with disease; LEEP: Loop Electrosurgical Exicision Procedure; LMP: lymphadenectomy; MRI: magnetic resonance imaging; MTX: methotrexate; NHL: non-Hodgkin lymphoma; NR: not reported; RH: radical hysterectomy; RT: radiotherapy; TAH: total abdominal hysterectomy; VAC: vincristine, doxorubicin and cyclophosphamide; VIA: etoposide, ifosfamide, cytarabine; VCR: vincristine; XRT: external beam radiation therapy.

Table II. *Distribution of treatment modality according to age and site of disease.*

	No. (%)	Mean age, years (min-max)
Total	144	51.58 (20-89)
Cervix	109 (75.7)	58.72 (26-89)
Corpus uteri	35 (24.3)	49.60 (20-85)
RT alone	7	55.57 (23-82)
Cervix	7 (100)	55.6 (27-82)
Corpus uteri	0 (0)	-----
CT alone	32	48.81 (20-81)
Cervix	25 (78.1)	45.7 (20-81)
Corpus uteri	7 (21.9)	59.6 (26-79)
Surgery alone	9	59.11 (35-89)
Cervix	2 (22.2)	57.5 (46-69)
Corpus uteri	7 (77.8)	59.6 (53-89)
Surgery+RT	11	53.18 (24-76)
Cervix	11 (100)	53.18 (24-76)
Corpus uteri	0 (0.0)	----
Surgery+CT	32	48.06 (31-78)
Cervix	21 (65.6)	44.75 (25-67)
Corpus uteri	11 (34.4)	54.09 (31-78)
RT+CT	44	53.72 (22-85)
Cervix	39 (90.7)	44.75 (25-66)
Corpus uteri	5 (11.6)	54.09 (31-78)
Surgery+RT +CT	2	42 (38-46)
Cervix	1 (50.0)	46
Corpus uteri	1 (50.0)	38
Treatment not reported	8	53.5 (24-68)
Cervix	4 (50.0)	42.25 (24-68)
Corpus uteri	4 (50.0)	64.75 (59-68)

CT: Chemotherapy; RT: radiotherapy.

days. After the aforementioned therapy, she achieved complete remission of the lymphoma. After 24 months, she is alive and disease free.

Materials and Methods

A bibliographic search on Medline (through PubMed) was conducted periodically from January 1990 to June 2013 for English articles and abstracts showing data on primary DLBCL of the uterus. No limits for type of article were set. A combination of the following medical subject headings or keywords used included: "diffuse large B-cell lymphoma" and "cancer", "cervix", "DLBCL", "mortality", "non-Hodgkin's lymphoma", "recurrence", "surgery", "treatment", "uterine cancer", "uterine carcinoma", "uterus", "vaginal bleeding". Titles and abstracts were initially screened, and potentially relevant articles were identified and reviewed for inclusion/exclusion criteria. Subsequently, protocols and results of the studies were examined according to specific inclusion criteria. Studies meeting the inclusion criteria were considered for the final analysis. Patients' characteristics and oncological data were recorded. In particular, data regarding patient age, clinical presentation, tumor site (cervix/corpus) and infiltration (vagina/parametrium/ pelvic wall), tumor subtype, Ann Arbor stage, and how diagnosis was made were recorded. Primary treatment and outcomes were noted. Specifically, primary treatment of the tumour,

Table III. *Oncological data.*

Total population	N	N	%
CR	105	144	72.9
DWD	17	144	1,4
AWD	2	144	11.8
Overall survival	107	144	74.31
NA	2	144	11.8
	Mean (months)	min	Max
CR	46.0	2	240
AWD	9.0	4	14
DWD	10.5	2	9
Overall survival	45.9	2	240
RT alone	N	N	%
CR	5	7	71.4
DWD	2	7	28.6
	Mean (months)	min	max
CR	81.6	6	240
DWD	22.5	7	38
CT alone	N	N	%
CR	23	32	71.88
DWD	4	32	12.5
AWD	1	32	3.13
Overall survival	24	32	75.0
NA	4	32	12.5
	Mean (months)	min	max
CR	25.74	4	72
DWD	9.75	1	18
AWD	14		
Overall survival	24.62	4	72
Surgery alone	N	N	%
CR	5	9	55.6
DWD	2	9	10.5
NA	2	9	22.2
	Mean (months)	min	max
CR	54	8	164
DWD	4	3	5
Surgery plus RT	N	N	%
CR	6	11	54.6
DWD	4	11	36.4
NA	1	11	9.1
	Mean (months)	min	max
CR	79.3	14	120
DWD	17.5	8	24
Surgery plus CT	N	N	%
CR	28	32	87.5
DWD	1	32	3.3
AWD	1	32	3.1
Overall survival	29	32	90.6
NA	2	32	6.3
	Mean (months)	min	max
CR	37.18	2	108
AWD	12		
DWD	4		
Overall survival	33.46	2	108
RT plus CT	N	N	%
CR	39	43	90.7
DWD	2	43	4.65
NA	3	43	6.98
	Mean (months)	min	max
CR	52.9	4	173
DWD	1.3	0.5	2
Surgery plus RT plus CT	N	N	%
CR	2	2	100
	Mean (months)	min	max
CR	33	30	36

Data are presented as number and percentage, or as mean with min-max values. AWD: Alive with disease; CR: cure rate; DWD: died with disease; NA: not assessed. Differences were not statistically significant, except for disease-free survival by surgery-alone *vs*. RT-plus-CT, p=0.032.

including chemotherapy, radiotherapy, and surgery, was noted. Efficacy data consisted of complete response (CR), alive with disease (AWD), died with disease (DWD), and died from other causes. In addition, the number and the site of recurrences were evaluated. Treatment of recurrences was also noted. All adjuvant treatments after first surgery, including type and dose, were recorded.

Continuous variables are expressed as the mean with minimum and maximum values, whereas categorical variables are expressed as number and percentage.

Results

A systematic review of the literature identified 143 cases of primary DLBCL of the uterus (Table I) (1-94). Table I reports the patients' characteristics. One hundred and eight cases (75.5%) of primary aggressive B-cell non-Hodgkin's lymphoma of the cervix (CE-DLBCL) and 35 (24.5%) cases of the CO-DLBCL were identified. The mean age of patients was 51.58 years (range=20-89 years): the mean age of patients with primary CE-DLBCL was 49.6 years (range=20-82 years), and in those with primary CO-DLBCL was 59.22 years (range=26-89 years). In 13.89% of cases, patients were asymptomatic (12.84% of primary CE-DLBCL and 17.4% of primary CO-DLBCL, respectively). Vaginal bleeding was present in 63.19% of cases (64.22% of primary CE-DLBCL and 60% of primary CO-DLBCL, respectively); abdominal/pelvic pain was present in 6.25% of cases (4.59% of CE-DLBCL and 11.43% of primary CO-DLBCL, respectively); multiple symptoms were present in 12.5% of cases (14.68% of CE-DLBCL and 5.71% of primary CO-DLBCL, respectively). Four cases (2.78%) presented different symptoms, and in two cases (1.39%) symptoms were not described. Macroscopic appearance of the lesions was variable, ranging from a little polypoid lesion to a huge mass of 20 cm in diameter. The diagnosis was reached at surgery (hysterectomy) in 15.28% of cases (13.76% of primary CE-DLBCL and 20% of primary CO-DLBCL, respectively). In 63.19% of all cases, primary uterus DLBCL was diagnosed at biopsy; in 12.5% of all cases it was suspected at imaging examinations; in 1.39% of all cases it was diagnosed by Pap smear; in 1.39% of all cases it was diagnosed at autopsy; in 1.39% of all cases it was suspected at clinical examination; in 4.86% of all cases, diagnosis was not reported. Staging of the 144 cases was as follows: stage I, 93 (64.58%); stage II, 25 (17.36%); stage III, 3 (2.08%); stage IV, 19 (13.19%). Stage was not reported in 4 (2.78%) cases.

The distribution of treatment modality according to age and site of disease is reported in Table II. The majority of patients received chemotherapy-alone [32/144 (22.22%)], or in combination with surgery [32/144 (22.22%)] or radiotherapy [44/144 (30.56%)]. Only 2/144 (1.39%) cases received chemotherapy with radiotherapy and surgery. No patient with primary CO-DLBCL received radiotherapy alone or in combination with surgery.

The mean overall survival was 45.9 months (range=2-240 months). Outcomes are reported in Table III. Follow-up data were not reported in 19/144 cases (13.2%) [13/109 (11.93%) of primary CE-DLBCL and 6/35 (17.14%) of primary CO-DLBCL]. After a follow-up period ranging from 3 days to 240 months, 2/125 (1.6%) patients were alive with disease [1/96 (1.04%) with primary CE-DLBCL and 1/29 (3.45%) with primary CO-DLBCL, respectively], 18/125 (14.4%) patients died [10/96 (10.42%) with primary CE-DLBCL and 7/29 (24.14%) with primary CO-DLBCL], and 106/125 (84.8%) patients were in complete remission [85/96 (88.54%) with primary CE-DLBCL and 21/29 (68.96%) with primary CO-DLBCL]. The median age of patients was 50.5 years, ranging from 20 to 85 years. In 73% of cases [106/125 (84.8%)], complete remission was achieved after a follow-up ranging from 4 to 240 months. In particular, 15/144 (10.4%) patients died of disease (nine with primary CE-DLBCL and six with primary CO-DLBCL); 10 patients died of progression after inadequate treatment (five with primary CE-DLBCL and five with primary CO-DLBCL); five patients died of relapse after complete remission (four with primary CE-DLBCL and one with primary CO-DLBCL, respectively). The median age of these patients was 42.6 years, ranging from 24 to 52 years. Early recurrence occurred in 5/125 (4%) cases within six months from primary treatment: two cases in the central nervous system, one case in the retroauricular and retroperitoneal lymph nodes, one case in the retroperitoneal and mesenteric lymph nodes and local recurrence, and one case as pelvic mass. Treatment of recurrences consisted of palliative therapy (three cases), chemotherapy (one case), and intrathecal methotrexate plus cytarabine and hydrocortisone plus whole brain irradiation (one case). The median age of patients with DLBCL who died was 56.7 years, ranging from 24 to 89 years. Three patients (2.4%) (one with primary CE-DLBCL and two with primary CO-DLBCL) died of other causes.

Discussion

Diagnosis of primary uterine lymphoma may be made through the unequivocal absence of nodal or other extranodal involvement at the time of presentation or (arbitrarily) three months before and three after diagnosis.

According to Vang *et al*., cervical involvement is more common than *corpus uteri* involvement (9). Prognosis depends on an accurate and timely diagnosis and the correct therapy. Unfortunately, diagnosis of primary CE-DLBCL is difficult and often delayed because of the rarity of the disease and of the absence of specific clinical symptoms (1-94). In fact, primary CE-DLBCL may occur in 70% of cases with non-specific vaginal bleeding. The difficulty of diagnosing cervical primary aggressive B-cell non-Hodgkin's lymphoma, as previously described (6, 10-11), is also confirmed by our report. The most common symptom was vaginal bleeding,

followed by non-specific abdominal/pelvic pain or no symptoms. Macroscopic appearance of the lesions was variable, ranging from a small polypoid lesion to a huge mass. Although biopsy was commonly diagnostic, sometimes it was less so because of the high incidence of benign lymphoid aggregates in this area (96). Furthermore, because DLBCL is a stromal disease, PAP smear was rarely diagnostic (1.39% of all cases) and was only able to diagnose this abnormality once ulceration of epithelial cells had occurred (5, 80).

Therapy is also still under debate, although several modalities of treatment have been reported in the literature. In the past, combined-modality treatment with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and moderate doses of radiation was considered the best treatment for NHL of the cervix (9, 12). Currently, although the role of chemotherapy associated to radiotherapy/surgery seems to be the gold standard in management of NHL of the cervix, some authors suggest an important role of monoclonal antibodies such as rituximab (2), active in NHL treatment binding the B-cell surface antigen CD20. Its use in DLBCL treatment was validated by the GELA trial, which showed that addition of rituximab to CHOP improved the overall survival of patients (13). The efficacy of rituximab in primary CE-DLBCL treatment has also been confirmed in more recent studies (2, 14). It is reported that primary NHL involving rare extranodal sites such as the uterus has a poor prognosis, with a median overall survival of slightly over 16 months (15); 5-year overall survival for patients with female genital tract NHL is 39.3% (14). In our review, the median overall survival was 45.9 months (range=2-240 months).

The IPI is usually considered the most reliable and reproducible prognostic model to quantify the prognosis of NHL, including extranodal NHL. The IPI model incorporates clinical features that reflect the growth and invasive potential of the tumor (tumor stage, serum lactate dehydrogenase (LDH) level, and number of extranodal disease sites), and the patient's ability to tolerate intensive therapy (age and performance status). In patients aged less than 60 years, the adjusted IPI is usually employed.

In our review, the site of the primary DLBCL seemed to be a prognostic factor. In fact, 88.54% of the primary CE-DLBCL presented a complete response compared with 68.96% of the primary CO-DLBCL. In the five relapses reported in our review, no specific patterns of relapse were identified. As in nodal lymphoma, intensive chemotherapy is recommended, followed by autologous stem cell transplantation. Although a previous review of the literature indicated that patients with genital primary aggressive B-cell non-Hodgkin's lymphoma were young (mean age=40 years) (2), our review of the data showed patients to be older (mean age=51.58 years, range=20-89 years) (Table II). Even if the comparison was not statistically significant (p=0.131), patients with primary CE-DLBCL were younger than those with primary CO-DLBCL (49.6 years, range=20-82 years, and 59.22 years, range=26-89 years, respectively). Even patients of reproductive age [41/144 (28.47%)] can be affected by DLBCL of the uterus. Correct diagnosis should be achieved to avoid the surgery that is required in the case of carcinoma or fibroids. Patients should be referred to specific counselling with a human reproduction specialist for a fertility preservation plan before starting CHOP chemotherapy. In fact, cyclophosphamide is the most gonadotoxic agent, inducing premature ovarian failure in 70% of cases, especially when combined with other chemotherapeutic drugs (16). However, some cases of pregnancy after treatment for CE-DLBCL treatment have been reported (97, 98). Over the last few decades in developed and developing countries, the incidence of extranodal NHL has increased more rapidly than it has for nodal NHL (17, 18). AIDS, immunosuppressive treatments, and lifestyle/environmental factors may explain this increase (17). Primary DLBCL of the cervix and CO are rare diseases but cannot be ruled out in cases when there are no specific clinical symptoms. The aim of our review is to raise the awareness of clinicians of these rare diseases and to try to identify the best way to treat them.

Despite the limitations of our review, such as it being a retrospective analysis, with inclusion of case series and case reports only, some missing data, heterogeneous treatments (most cases were pre-rituximab) and evolution of classification systems over the study period, certain recommendations emerged from it. Primary CE-DLBCL is more common than primary CO-DLBCL and occurs in younger patients; primary CE-DLBCL presents a better prognosis than does primary CO-DLBCL; the most common symptom is vaginal bleeding; in the presence of uterine bleeding and/or enlargement, or uncertain cytology, once other common causes have been excluded, the diagnosis of primary uterine DLBCL should be considered. Histological examination is essential for diagnosis; a biopsy is the most common and most useful method to reach diagnosis. When a primary uterine DLBCL is diagnosed, all staging investigations must be carried-out (CT, PET scan, bone marrow biopsy) to make sure that it is a primary lymphoma of the uterus; the Ann Arbor staging system should be used; the most common stage is I. Immunochemotherapy (rituximab+CHOP or CHOP-like regimen) with/without radiotherapy is the most common and most effective treatment; surgery should be avoided. Fertility-sparing treatment should be guaranteed (oocyte retrieval before starting chemotherapy) whenever possible. There are no specific patterns of relapse in patients with primary DLBCL of the uterus.

In our opinion, gynaecologists who suspect either of these diseases should work closely with other specialists (gynaecologist, haematologist, pathologist, and human reproduction specialist) either to rule-out primary DLBCL of the uterus, or to reach a rapid, efficient, and accurate diagnosis. This multi-disciplinary approach saves time, allows

planning of the most adequate therapy (thereby avoiding needless surgery), and can provide the patient with specialist counselling for a fertility-preservation program, should the need arise.

Conflicts of Interest

The Authors declare that they have no competing interests.

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