Ocular adnexal lymphoma—comparison of MALT lymphoma with other histological types

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Abstract

Aims—To correlate histological features of ocular adnexal lymphoma using the revised European American lymphoma classification (REAL), with stage of disease at presentation, treatment modalities, and patient outcome. MALT lymphoma defines an extranodal marginal zone B cell lymphoma as outlined in the REAL classification. Comparison groups of patients included those with primary ocular adnexal MALT lymphoma versus primary ocular adnexal lymphomas of other types, MALT lymphoma versus non-MALT lymphomas (primary and secondary), and primary ocular adnexal lymphoma (MALT lymphomas and other types) versus secondary ocular adnexal lymphomas.

Methods—A retrospective review of the National Ophthalmic Pathology Laboratory records identified 20 cases of ocular adnexal lymphoma over a 10 year period which were reclassified using appropriate immunohistochemical stains. Patients' medical records were examined for data including stage of the disease at presentation, mode of treatment, and patient outcome.

Results—Among the 20 cases identified 14 had primary ocular adnexal lymphomas. 10 of the primary lymphomas had histological features of MALT lymphoma. One case was a primary ocular adnexal T cell lymphoma, one a follicular centre, follicular B cell lymphoma, and two were large cell B cell lymphomas. Six cases had systemic disease, four large B cell, one follicular centre, follicular B cell, and one mantle cell. A significantly higher proportion of patients with MALT lymphomas had early disease ($p = 0.005$), initially required local treatment ($p = 0.005$) and were alive at last follow up ($p = 0.001$) than those without. Two patients with MALT lymphoma had recurrence of lymphoma which responded to further treatment.

Conclusions—Patients with primary ocular adnexal MALT lymphomas present with localised disease requiring local treatment and have a better outcome compared with patients with other types. As a small percentage of these tumours recur, patients should be followed up indefinitely.

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sue, or lacrimal structures. Pathological diagnosis is based on routine light microscopy supported by immunohistochemical staining (or molecular genetic analysis) to identify lineage.¹ The presence of light chain restriction (cells expressing only one immunoglobulin light chain) is characteristic of B cell lymphomas, but differentiation between benign and malignant lesions may be extremely difficult on small biopsies.¹ The majority of ocular adnexal lymphomas are non-Hodgkin's B cell lymphomas and by definition are extranodal lymphomas. Older classifications of lymphomas, including the working formulation,² and the Kiel classification,³ referred to lymphomas originating in lymph node sites but did not recognise extranodal lymphomas as distinct clinical entities resulting in inappropriate classification of some tumours. Lymphomas arising at extranodal sites are relatively common accounting for between 24% and 48% of lymphomas and besides ocular adnexal lymphomas also include peripheral T cell lymphomas such as mycosis fungoides.^{4,5}

The new revised European American lymphoma classification (REAL) of lymphoid malignancy first proposed by the International Lymphoma Study Group differs from older classifications in recognising these new entities and is not only based on classic histological criteria but also clinical, immunohistochemical, and molecular genetic data.⁶ The REAL classification in many instances condensed a number of terms used in the previous classifications into one group with or without a small number of provisional subgroups as highlighted in Table 1. Included in the extranodal group of lymphomas are marginal zone B cell lymphoma of MALT (mucosal associated lymphoid tissue) type or MALT lymphomas.

MALT lymphomas are characterised by cellular heterogeneity including small lymphocytes with moderate amount of pale cytoplasm and typically irregular or cleaved nuclei (centrocyte-like lymphocytes) and small round lymphocytes. Monocytoid B cells, plasma cells, and the occasional large cell are also seen. The diagnosis of MALT lymphomas can be difficult and histologically in the early stages they exist as an infiltrate between pre-existing reactive follicles which they can overrun (follicular colonisation). Similarly, lymphoma cells may infiltrate overlying mucosal surfaces with subsequent inclusion of epithelial islands (lymphoepithelial lesions). MALT lymphomas may be acquired secondary to autoimmune disease or infection at a given site providing the substrate for lymphoma development. These lymphomas were first

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Ocular adnexal lymphoid tumours may involve the eyelids, conjunctiva, orbital connective tis-

Table 1 Comparison of selected subtypes in three classifications (modified from Harris et al⁶)

REAL classification ⁶	Working formulation ³	Updated Kiel classification ²
Extranodal marginal zone B cell lymphoma (low grade B cell lymphoma of MALT type)	<i>Small lymphocytic*</i> Diffuse, small cleaved cell	No equivalent
Lymphoplasmacytoid lymphoma	Diffuse, mixed small and large cell Small lymphocytic plasmacytoid <i>Diffuse, mixed small and large cell</i>	Lymphoplasmacytic immunocytoma
Follicular centre lymphoma, diffuse, small cell	Diffuse, small cleaved cell	Centroblastic-centrocytic, diffuse
Follicular centre lymphoma, follicular	<i>Follicular, predominantly small, large, or mixed cells</i> <i>Follicular, mixed small and large cells</i> Follicular, predominantly large cell	Centroblastic-centrocytic, follicular
Diffuse large B cell lymphoma	<i>Diffuse, large cell</i> Large cell immunoblastic	Centroblastic or B immunoblastic
Mantle cell lymphoma	Diffuse, mixed small and large cell <i>Diffuse, small cleaved cell</i> Small lymphocytic	<i>Centrocytic</i> Centroblastic, centrocytoid subtype
Peripheral T cell lymphomas, unspecified	Follicular, small cleaved cell, Diffuse, mixed small and large cell Diffuse, large cleaved cell Diffuse, mixed small and large cell	Pleomorphic, medium sized and large T cell

*When REAL category is equivalent to more than one working formulation or updated Kiel category, italicised category comprises the majority of cases.

described in the mucosal tissue of the stomach⁷⁻⁹ and typical histological changes have also been documented in lymphomas of lung, salivary gland, thyroid, and conjunctiva.¹⁰⁻¹⁴ As the criteria for diagnosis of MALT lymphomas have become more defined (partially because of the availability of suitable immunohistochemical stains), histologically similar primary tumours have been identified in non-mucosal sites (that is, tissues without an overlying epithelium) such as orbital soft tissue.¹⁵⁻¹⁷ MALT lymphomas are thought to have an indolent natural history and respond well to radiotherapy.¹⁷⁻¹⁹ They may recur, however, and the site of recurrence may be another typical MALT site.¹⁴⁻¹⁷

A number of previous studies have attempted to correlate pathological diagnosis with clinical outcome in both lymphoid hyperplasia and malignant lymphoma of ocular adnexal tissues, but these were carried out before the advent of the REAL classification.²⁰⁻²⁶ However, these studies do identify a subgroup of lymphomas of small, well differentiated lymphocytes that had an indolent course. A recent clinicopathological study which focused on identifying MALT lymphomas found that, although a high proportion of ocular adnexal lymphomas had MALT characteristics, there was no significant difference between outcome in patients with MALT lymphomas and those with other histology.¹⁷ The current study was designed to correlate pathological diagnosis with clinical outcome of patients with ocular adnexal lymphoma in patients with a variety of histological subtypes.

Materials and methods

A retrospective clinicopathological study of ocular adnexal lymphoma referred on a nationwide basis to the National Ophthalmic Pathology Laboratory located in the Royal Victoria Eye and Ear Hospital over a 10 year period was undertaken. Using the National Ophthalmic Pathology register relevant cases were identified and the biopsy preparations were re-examined and reclassified according to the REAL classification. The reclassification was based on morphological features seen on routinely prepared slides of tissues fixed in formalin and embedded in paraffin wax. Immu-

nophenotyping was carried out on fixed sections using the avidin-biotin peroxidase conjugate method²⁷ and the Vector elite kit (Vector Laboratories, Burlingame, CA, USA). Normal tonsillar tissue served as a positive control for immunohistochemistry. Negative controls comprised of omission of the primary antibody and its replacement by serum on a duplicate section of the lymphoma to be tested. Immunohistochemical stains used included CD 20 (1:100, Dako Corporation, Santa Barbara, CA, USA) (to identify B lymphocytes), CD3 (1:50) (Dako Corporation), and CD45 RO (1:50, Dako Corporation) to identify T lymphocytes, CD21 (1:10, Dako Corporation), which demonstrates the dendritic skeleton of lymphoid follicles while Cytokeratin stain (undiluted, Becton Dickinson, San Jose, CA, USA) highlighted characteristic invasion of mucosal surfaces by lymphocytes. Selected cases were stained with CD 5 and CD 10 (1:100, 1:40 respectively, both from Novocastra, Newcastle upon Tyne) which can help differentiate between MALT lymphoma and other B cell neoplasms such as mantle cell lymphoma or follicular lymphomas. Rabbit antibodies to human immunoglobulin kappa and lambda light chains (1:300, 1:1000 respectively, Dako Corporation) were used to determine monoclonality. All the antibodies used were monoclonal with the exception of CD3 which was polyclonal. While the more recent cases had the immunohistochemistry done at the time of diagnosis, the majority of the cases required new samples to be cut from stored paraffin blocks for newer antibodies to be applied.

Disease was defined as primary ocular adnexal lymphoma provided no evidence of extraorbital disease was detected following a staging evaluation when a pathological diagnosis of lymphoma within the orbit was made. Staging evaluation included full blood count, differential white cell count, platelet count biochemical profile, bone marrow aspirate and biopsy, computed tomography (CT) scan (and/or magnetic resonance imaging) of the orbits along with CT examination of thorax and abdomen. Those patients with disease outside the orbits were classified as having dis-

Figure 1 (A) Photomicrograph of conjunctival MALT lymphoma, demonstrating a monotonous infiltrate of small round and small cleaved lymphocytes. The remnant of a pre-existing germinal centre has been colonised by tumour cells (large arrow) (haematoxylin and eosin $\times 40$). (B) Photomicrograph of conjunctival MALT lymphoma, stained with the immunohistochemical stain for follicular dendritic cell delineates the skeleton of a pre-existing germinal centre (large arrow) (CD21 $\times 40$). (C) Photomicrograph of conjunctival MALT lymphoma, stained with immunohistochemical stain outlining a lymphoepithelial lesions (a) and highlighting lymphocytic invasion of the mucosal surface (large arrow) (cytokeratin $\times 400$). (D) Photomicrograph of conjunctival MALT lymphoma, stained with an immunohistochemical T cell marker, demonstrating the typically high percentage of T cells in these tumours. Many of the epithelial infiltrating lymphocytes are of T cell phenotype (small arrows) (CD3 $\times 40$).

seminated lymphoma with orbital involvement labelled secondary ocular adnexal lymphoma.

Treatment modalities consisted of local excision alone, local excision with radiotherapy, radiotherapy alone, chemotherapy alone, or chemotherapy combined with radiotherapy. In terms of outcome patients were classified as alive without disease, alive with active disease, deceased secondary to lymphoma, or deceased secondary to other causes. Evaluation of disease stage, mode of treatment, and outcome required input from ophthalmologists and oncologists to whom patients had been referred for further evaluation and treatment.

Patients were categorised into three groups including those with primary ocular adnexal MALT lymphomas (group 1), patients with primary ocular adnexal lymphomas of other types (group 2), and patients with systemic lymphomas with orbital manifestations either at presentation or relapse (group 3). The significance of any differences between these groups with regard to stage of disease at presentation (when applicable), mode of initial treatment, and patient outcome was analysed using the Fisher exact test.

Results

Twenty cases of ocular adnexal lymphoma were identified from the records of the

National Ophthalmic Pathology Laboratory. Of these, 12 were male and eight were female (ratio 1.7:1) while the mean age of the patients was 62.2 years (median 62.0 years; range 35–82 years). The majority had primary lymphoma arising within the ocular adnexae ($n = 14$), with the remainder being sites of disseminated lymphoma within ocular adnexal tissue ($n = 6$) (Table 2).

HISTOLOGICAL DIAGNOSIS

The majority of patients in the primary lymphoma group had histological features of MALT lymphoma ($n = 10$), while one patient had a primary T cell lymphoma of the medial canthus. Of the six patients in the secondary lymphoma group, four had diffuse large B cell lymphoma, one had follicular centre, follicular B cell lymphoma, and one had mantle cell lymphoma (Table 2). According to the working formulation, seven of the MALT lymphomas had previously been classified as small lymphocytic, (diffuse, small, cleaved cell) lymphomas, two were designated as small lymphocytic plasmacytoid lymphoma, and the last as a diffuse, small cleaved cell lymphoma.

Histological examination of the MALT lymphomas revealed a diffuse infiltrate of small cleaved centrocyte-like lymphocytes. A vaguely nodular pattern was seen as a result of follicu-

Table 2 Summary of cases

Case	Patient age (years)	Histological type (REAL)	Site of lesion	Presenting complaint	Symptoms duration (months)	Initial treatment	Follow up (years)	Patient outcome
Group 1: Primary ocular adnexal MALT lymphoma								
1	35	MALT lymphoma	Right orbit	Diplopia, proptosis	1	Local excision, Radiotherapy (25 Gy)	8	Alive and well
2	65	MALT lymphoma	Left orbit	Diplopia, pain, proptosis	3	Local excision, Radiotherapy (28 Gy)	5	Alive and well
3	71	MALT lymphoma	Left orbit	Proptosis, soft tissue swelling	9	Local excision, Radiotherapy (45 Gy)	3	Alive and well
4	50	MALT lymphoma	Right orbit	Soft tissue swelling	1	Local excision	2	Alive and well
5	45	MALT lymphoma	Right orbit	Diplopia, proptosis	4	Local excision	2	Alive and well
6	48	MALT lymphoma	Left lower lid	Palpable mass	Unknown	Local excision	6	Alive and well (Treated recurrence, 2 years)
7	72	MALT lymphoma	Right upper lid	Palpable mass	12	Local excision	5	Deceased secondary other cause
8	54	MALT lymphoma	Right conjunctiva	Pain, ptosis	18	Local excision, Radiotherapy (27 Gy)	4	Alive and well (Treated recurrence, 18 months)
9	73	MALT lymphoma	Left conjunctiva	Palpable mass	Unknown	Local excision, Radiotherapy (30 Gy)	1	Alive and well
10	48	MALT lymphoma	Right conjunctiva	Incidental finding	Unknown	Local excision, Radiotherapy (30 Gy)	1	Alive and well
Group 2: Primary ocular adnexal lymphoma of other type								
11	62	Diffuse, large B cell	Left orbit	Diplopia, soft tissue swelling	Unknown	Chemotherapy (CHOP)	7	Alive and well
12	75	Diffuse, large B cell	Right orbit	Proptosis	Unknown	Radiotherapy (30 Gy), Chemotherapy (CHOP)	3	Deceased secondary lymphoma
13	61	Follicular centre lymphoma, follicular	Right orbit	Diplopia, proptosis	2	Radiotherapy (30 Gy)	0.5	Alive and well
14	59	Peripheral T cell lymphoma—unspecified	Right medial canthus	Palpable mass	9	Radiotherapy (28 Gy), Chemotherapy (CHOP)	7	Alive and well
Group 3: Secondary ocular adnexal lymphoma								
15	72	Diffuse, large B cell	Left orbit	Proptosis, ptosis	3	Radiotherapy (25 Gy)	1	Deceased secondary lymphoma
16	72	Diffuse, large B cell	Left orbit	Proptosis, soft tissue swelling	2	Radiotherapy (30 Gy), Chemotherapy (CHOP)	1	Deceased secondary lymphoma
17	78	Diffuse, large B cell	Left orbit	Pain, proptosis	2	Chemotherapy (CHOP)	1	Alive and well
18	78	Diffuse, large B cell	Right orbit	Proptosis	3	Radiotherapy (25 Gy)	0.5	Deceased secondary lymphoma
19	82	Follicular centre lymphoma, follicular	Left lower lid	Palpable mass	6	Local excision	0.5	Deceased secondary lymphoma
20	57	Mantle cell (B cell)	Right conjunctiva	Pain	3	Chemotherapy (CHOP, DHAP, cisplatin and fludarabine)	0.5	Deceased secondary lymphoma

lar colonisation which is the remnants of pre-existing benign reactive lymphoid follicles overrun by neoplastic small centrocyte-like cells (Fig 1A). Follicle remnants were demonstrated by CD 21 stain which outlined residual dendritic reticular networks in all cases (Fig 1B). The majority of the small cleaved cells were immunoreactive for the B cell marker CD20 and were negative for CD5 and CD10. Small round lymphocytes scattered throughout were immunoreactive for T cell markers CD3, CD45, and CD5 (Fig 1C). T cells were also present within the overlying conjunctival epithelium. Other typical features included occasional germinal centres with obvious mantle zones and both multinucleate dendritic cells and plasma cells were prominent in many of the biopsies. The plasma cells consisted both of tumour cells with plasmacytoid differentiation (light chain restricted on immunohistochemistry) and polyclonal plasma cells, which were prominent in two thirds of cases. In three cases with conjunctiva included, lymphoepithelial lesions were seen characterised by lymphocytic invasion of the mucosal surface demonstrated with cytokeratin stain (Fig 1D). Seven of the MALT lymphomas expressed monotypic immunoglobulin, five positive for kappa light chain and two positive for lambda light chain. In three MALT lymphomas assessment of immunoglobulin was not possible owing to

technical difficulties and the diagnosis was based on the typical histological findings as outlined above supported by immunostaining demonstrating lesional cells of predominant B cell origin positive for CD20 but negative for CD5 and CD10.

The diagnosis of the non-MALT lymphomas was based on typical histological features and appropriate expected immunohistochemical findings using the same panel of antibodies and in the case of secondary involvement by previously diagnosed lymphoma, review of and comparison with previous material.

SITE OF LESIONS, PRESENTING SYMPTOMS

The majority of the lymphomas were located in the orbital connective tissues ($n = 12$). There were no lacrimal gland lymphomas. Presenting symptoms were related to the location of the tumour mass within the adnexal tissues (Table 2). The most common presenting symptom was proptosis ($n = 11$) and half the patients had more than one presenting symptom. The mean duration between first symptom and presentation was 5.2 months (median 3 months; range 1–18 months) (Table 2).

STAGING OF DISEASE

Accurate data regarding staging of disease were available in the majority of patients, 18 of 20. Eight of 10 patients with MALT lymphoma were fully staged and all of these had disease

confined to the orbit (Table 2). The remaining two patients had localised disease based on clinical evaluation. Among the 10 patients who did not have MALT lymphoma, four were defined as belonging to group 2—that is, primary ocular adnexal lymphoma other than MALT lymphoma, and six as belonging to group 3 (secondary ocular adnexal lymphoma as a manifestation of disseminated disease) (Table 2).

TREATMENT OF DISEASE

All patients with MALT lymphoma had localised treatment with excision of the lesion alone ($n = 4$) or combined with local radiotherapy in doses ranging from 25 Gy to 46 Gy ($n = 6$) (Table 2). CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy alone or in combination with local radiation (28–30 Gy) was administered to three of the four patients in group 2, two of whom had diffuse large B cell lymphoma, while the third had a peripheral T cell lymphoma unspecified. The fourth patient with follicular cell, follicular B cell lymphoma had local radiation (30 Gy) (Table 2). The six patients in group 3 with disseminated disease were treated with various modalities and combinations of treatments. Four elderly patients with diffuse B cell lymphoma received either CHOP ($n=2$) or palliative radiotherapy (25 Gy, $n=2$), while an 82 year old woman with follicular centre, follicular B cell lymphoma was treated with surgical excision only. The sixth patient had disseminated mantle cell lymphoma and was treated with a range of chemotherapies including oral chlorambucil, COP (cyclophosphamide, vincristine, prednisolone), CHOP, DHAP (dexamethasone, cytosine arabinoside, and cisplatin) and cisplatin combined with fludarabine (Table 2).

PATIENT OUTCOME

Those patients with primary ocular adnexal MALT lymphoma had a mean duration of follow up of 3.7 years (median 3.5 years; range 1–8 years), patients in group 2 had a mean follow up of 4.4 years (5 years; 0.5–7 years) and group 3 had a mean follow up of 0.75 years (0.75 years; 0.5–1 year). The majority of patients with MALT lymphoma are alive ($n=9$) but one patient has died of an unrelated cause. Two patients with MALT lymphoma had recurrence of disease, one in the gastric mucosa and psoas muscle at 3 years' follow up, and the other in ocular adnexal tissues 2 years after initial treatment. Both patients responded to further treatment (CHOP chemotherapy in the case of gastric mucosa/psoas muscle involvement and local radiation therapy in the patient with adnexal recurrence). Three of the four patients in group 2 are alive and free of disease while one has died of malignant lymphoma. Five of the six patients with disseminated lymphoma have died while one is alive and well following chemotherapy (Table 2).

COMPARISON BETWEEN PATIENT GROUPS

A significantly higher proportion of patients with MALT lymphoma initially required local treatment ($p = 0.01$) than patients with other histological types of primary ocular adnexal lymphoma and although a larger proportion of patients with primary MALT lymphoma were alive at last follow up the difference was not significant. A significantly higher proportion of patients with MALT lymphoma presented with local disease ($p = 0.005$), initially required local therapy ($p=0.005$) and were alive at last follow up ($p = 0.001$) than patients with all other histological types of lymphoma (both primary and secondary). A higher proportion of patients with all types of primary lymphoma received local treatment than patients with disseminated disease although the difference was not significant but a significantly higher percentage of patients with primary lymphoma (all types) were alive at last follow up ($p = 0.002$).

Discussion

This study has concentrated on patients with malignant ocular adnexal lymphoma, while earlier studies have included patients with histologically benign and indeterminate lymphoid proliferations,^{20–26} which can make comparison of results difficult. Furthermore, few previous papers include MALT lymphoma as a histologically distinct entity.^{16, 17} In this study, immunohistochemistry demonstrated that all of the included cases of ocular adnexal lymphoma except one, were B cell lymphomas. The case in question presented as a localised eyelid tumour which was fully staged and histologically confirmed to be a peripheral T cell lymphoma unspecified. There has been no evidence of systemic disease on long term follow up. While patients with mycosis fungoides may have involvement of the ocular adnexal tissues,²⁸ there is only one previously recorded case of a primary T cell lymphoma of the ocular adnexal tissues.²⁹ The case included in our review supports the view that although rare, primary ocular adnexal lymphomas may be of T cell type, a fact disputed by previous authors.²⁵

Involvement of particular adnexal tissues produces characteristic presenting symptoms and/or clinical signs. The most common presenting symptom was proptosis. This reflected orbital involvement in the majority of patients and all patients with the most frequent combination of symptoms, proptosis, and diplopia also had orbital deposits. In contrast, all patients with lid lesions presented with a palpable mass while those with conjunctival lesions had a variety of presenting complaints. A similar spectrum has been documented in a previous study.¹⁷ This study, unlike a number of earlier reports did not find a high incidence of conjunctival disease in cases of MALT lymphoma.^{24, 25}

While the staging procedures used varied and were not complete in all patients, patients with MALT lymphoma were more likely to have localised disease at presentation. Previous reports disagree as to whether MALT

lymphoma can occur as primary disease, or as both primary and secondary disease in the ocular adnexa.^{16 17} Staging procedures measure the extent of disease and along with histology and performance status determine the treatment approach. Results frequently reflect long term patient outcome. Patients in this study with localised disease and histologically low grade lymphomas received local treatment, an approach similar to that described in previous studies.^{17 25} We suggest that all patients with ocular adnexal lymphoma undergo a staging protocol which includes full blood count, differential white cell count, platelet count, full biochemical profile including lactate dehydrogenase levels, bone marrow aspirate, and biopsy with CT scan of head and body. This protocol would normally involve assessment by an oncologist or haematologist.

As in previous studies patients with primary ocular adnexal lymphoma included in this study had a better outcome than those with secondary disease.^{17 20-22 24-26} Furthermore, when compared with other histological types of lymphoma a significantly higher proportion of MALT lymphoma patients in this study presented with local disease, initially required local treatment, and were alive at last follow up. This is in contrast with a recent study which included MALT lymphoma as a distinct histological type where no significant difference in outcome was seen between MALT lymphoma patients and those with other primary lymphomas.¹⁷ As evidenced by the two cases reported in this study, all MALT lymphomas have the potential to recur at other MALT sites but the histology at recurrence is generally similar to the initial lesions.^{14 15} This tendency is probably due to specific circulation and homing patterns characteristic of lymphocyte subtypes.^{30 31} While the number of patients presented here is small, the clinical inference is that the histological recognition of MALT features is important as patients with MALT lymphomas have a more favourable outcome but require indefinite follow up.^{16 17}

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