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CASE REPORT

Angioimmunoblastic T-cell lymphoma: case report demonstrating the utility of molecular mutational analysis

Linfoma angioinmunoblástico de células T: informe de un caso que demuestra la utilidad del análisis mutacional molecular

Linfoma de células T angioimunoblástico: relato de caso demonstrando a utilidade da análise mutacional molecular

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ABSTRACT

Angioimmunoblastic T-cell lymphoma is a distinctive, yet rare, peripheral T-cell lymphoma. In the United States, the incidence is approximately 0.05 cases per 100,000 person-years, representing 15% to 20% of peripheral T-cell lymphomas and 1% to 2% of non-Hodgkin lymphomas. A 62-year-old man with systemic symptoms and diffuse lymphadenopathy was presented. The neoplastic cells lacked CD10/BCL6, but showed strong expression of PD-1, ICOS and CXCL13, and harbored mutations in TET2 and DNMT3A, confirming a follicular helper T-cell phenotype. Expanded TFH immunostaining, combined with targeted mutational analysis, can resolve diagnostically ambiguous AITL presentations.

Keywords: T-Cell lymphoma; peripheral T-cell lymphoma; molecular pathology

RESUMEN

El linfoma angioinmunoblástico de células T es una entidad distintiva dentro de los linfomas periféricos de células T, aunque poco frecuente. En los Estados Unidos, su incidencia anual se estima en aproximadamente 0,05 casos por cada 100 mil habitantes, lo que representa entre el 15 % y el 20 % de los linfomas periféricos de células T y entre el 1 % y el 2 % de los linfomas no Hodgkin. Se describió paciente masculino de 62 años con síntomas sistémicos y linfadenopatía generalizada. Las células neoplásicas mostraron ausencia de expresión de los marcadores CD10 y BCL6, pero una marcada positividad para PD-1, ICOS y CXCL13. El estudio molecular evidenció mutaciones en TET2 y DNMT3A, confirmándose un fenotipo de células T foliculares auxiliares. La combinación de un perfil inmunofenotípico compatible con células TFH y el análisis genómico puede resultar fundamental para resolver casos con características morfológicas o inmunohistoquímicas atípicas.

Palabras clave: infoma de células T; linfoma periférico de células T; patología molecular

RESUMO

O linfoma angioimunoblástico de células T (AITL) é um linfoma de células T periférico distinto, porém raro. Nos Estados Unidos, a incidência é de aproximadamente 0,05 casos por 100.000 pessoas-ano, representando 15% a 20% dos linfomas de células T periféricos e 1% a 2% dos linfomas não Hodgkin. Se descreve um homem de 62 anos com sintomas sistêmicos e linfadenopatia difusa. As células neoplásicas não apresentavam CD10/BCL6, mas apresentavam forte expressão de PD-1, ICOS e CXCL13, e apresentavam mutações em TET2 e DNMT3A, confirmando um fenótipo de célula T auxiliar folicular (TFH). A imunocoloração expandida de TFH, combinada com análise mutacional direcionada, pode resolver apresentações de AITL com diagnóstico ambíguo.

Palavras-chave: linfoma de células T; linfoma de células T periférico; patologia molecular

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INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL), now termed “nodal T-follicular helper cell lymphoma, angioimmunoblastic-type” in the 5th edition WHO classification and the 2022 International Consensus Classification (ICC), is the prototypic lymphoma derived from germinal-centre T-follicular helper (TFH) cells.(1) It accounts for approximately 15% – 20% of peripheral T-cell lymphomas (PTCLs) and 1% – 2% of all non-Hodgkin lymphomas (NHL).

Diagnostic criteria require nodal architecture effacement by a TFH-cell proliferation, demonstrating at least two TFH markers: PD-1, ICOS, CXCL13, CD10 or BCL6, together with characteristic high-endothelial venule and follicular dendritic-cell (FDC) expansion.

AITL is uncommon but shows geographic variability: the age-adjusted incidence is approximately 0.05 per 100.000 persons-years in North America(1), 0.03–0.06 in Western European population-based registries(2), and up to 0.09 in selected East-Asian cohorts.(3) In the United States, Surveillance, Epidemiology, and End Results (SEER) data indicate that AITL represents approximately 1.7% of new NHL diagnoses annually.

The median age at presentation is 65-70 years, and there is a mild male predominance (male-to-female ratio≈1.3:1). Epidemiologic studies further highlight associations with clonal haematopoiesis of indeterminate potential, particularly involving TET2 or DNMT3A, and an increased incidence of concurrent or metachronous myeloid neoplasms (2% – 10%).

Patients typically present with rapidly progressive, generalized lymphadenopathy, accompanied by "B-symptoms" (fever, night-sweats, weight loss). Immune dysregulation is a hallmark, and may manifest as pruritic rash, polyarthritis, capillary leak with oedema, autoimmune cytopenias or polyclonal hypergammaglobulinaemia. Laboratory abnormalities frequently include anaemia, elevated lactate dehydrogenase, eosinophilia and a positive direct Coombs test. Extranodal disease is common (spleen, liver, skin, pleural/ascitic effusions), and bone-marrow involvement is detected in up to 60% of cases. Without risk-adapted therapy, median overall survival (OS) with CHOP-like chemotherapy is only 20 – 30 months.[4]

AITL arises from TFH cells that have accumulated a multistep series of genetic lesions. Early epigenetic hits in TET2 and DNMT3A are present in approximately 80% and approximately 35% of cases, respectively, and often occur in haemopoietic stem cells, explaining the frequent detection of identical mutations in non-tumour cells and their linkage to clonal haematopoiesis. A subsequent "second-hit" mutation in RHOA (G17V) is detected in 50 % – 70% of AITL and induces aberrant T-cell signalling and TFH polarisation, while the hotspot IDH2 R172 substitution (present in 20% – 30%) confers high disease specificity. Additional alterations in PLCG1, CD28, VAV1 and copy-number gains of TNFRSF14, further dysregulate T-cell receptor and co-stimulatory pathways. The TFH-derived cytokine milieu (IL-21, IL-4, CXCL13) fosters expansion of EBV-positive B-immunoblasts and FDC networks, producing the polymorphous histology that typifies AITL.

Accurate diagnosis hinges on integration of morphology, an expanded TFH immunohistochemical panel and targeted NGS. Recognition of the underlying molecular landscape has therapeutic relevance: TFH lymphomas harbouring epigenetic mutations demonstrate heightened sensitivity to histone deacetylase inhibitors and hypomethylating agents, and ongoing trials are evaluating combination strategies with PI3Kδ/γ inhibitors, anti-CD30 antibody-drug conjugates and immune checkpoint blockade.

CASE PRESENTATION

A 62-year-old man with prior resection of colonic adenocarcinoma presented with fever, night-sweats, 5-kg weight loss and generalized lymphadenopathy of two-months' duration. Examination showed bilateral axillary, supraclavicular and inguinal lymphadenopathy and a faint maculopapular rash.

Laboratory data: Hb 10.7 g/dL; WBC 3.4 × 10^9/L (neutrophils 55%, lymphocytes 25%, eosinophils 6%); platelets 142 × 10^9/L; LDH 192 U/L (ULN 280 U/L); serum IgG 2.300 mg/dL. Direct Coombs test negative.

Imaging: CT-PET demonstrated splenomegaly (16 cm) and FDG-avid lymphadenopathy (maximum SUV 12.4) without extranodal uptake. Staging: Ann Arbor stage IIIA; ECOG 1.

Pathologic findings

Excisional biopsy of the 5 cm left-axillary node revealed complete effacement of the nodal architecture by a polymorphous infiltrate of medium-sized lymphoid cells with pale, clear cytoplasm. Figure 1 (H&E Section) shows numerous arborizing high-endothelial venules coursed through the lesion, and the follicular dendritic-cell meshwork was conspicuously expanded and highlighted by CD23. Scattered immunoblasts were present, whereas multinucleated Reed–Sternberg-like cells were absent.

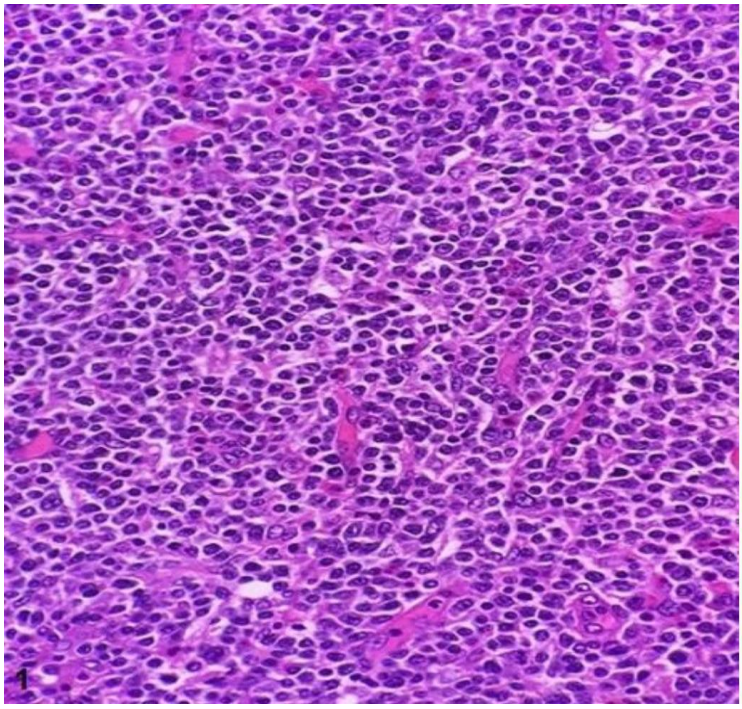

Fig. 1. Lymph node biopsy shows effacement of normal nodal architecture and replacement by monotonous atypical lymphoid cells and prominent arborization of the blood vessels. H&E x200 magnification.

The immunophenotypic profile of the neoplastic T cells is summarized in Table 1.

Table 1. Immunophenotypic profile of neoplastic T cells

Marker	Result	Interpretation
CD2,3,5	Diffusely positive	Pan T-cell marker
CD4	Strongly positive	Helper T-cell bias
CD8	Scattered positive cells	Reactive cytotoxic T-cells
PD-1	Positive	TFH marker
CXCL13	Positive	TFH marker
ICOS	Positive	TFH marker
CD10 and BCL6	Negative	Atypical
CD20 and PAX5	B-cells positive	Residual follicles
CD30	Negative	Aid in differential diagnosis
EBER-ISH	Scattered positive cells	

Diffuse PD-1 Figure 2 (PD-1 IHC) and CD4 Figure 3 (CD4 IHC), strong ICOS Figure 5 (ICOS IHC) and patchy CXCL13 Figure 4 (CXCL13 IHC) expression confirm a TFH phenotype, thereby fulfilling the 2016 WHO criterion for nodal TFH-cell lymphoma, angioimmunoblastic type.

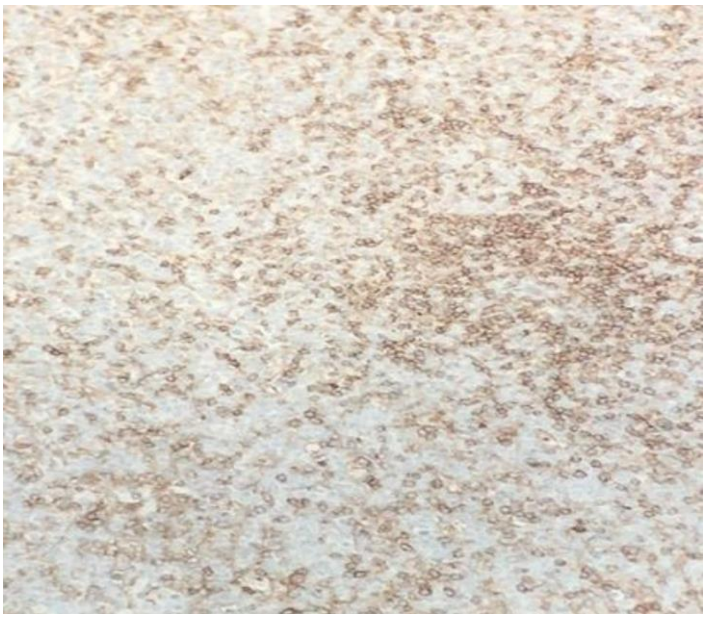

Fig. 2. Immunohistochemistry (IHC) PD-1 (x200 magnification).

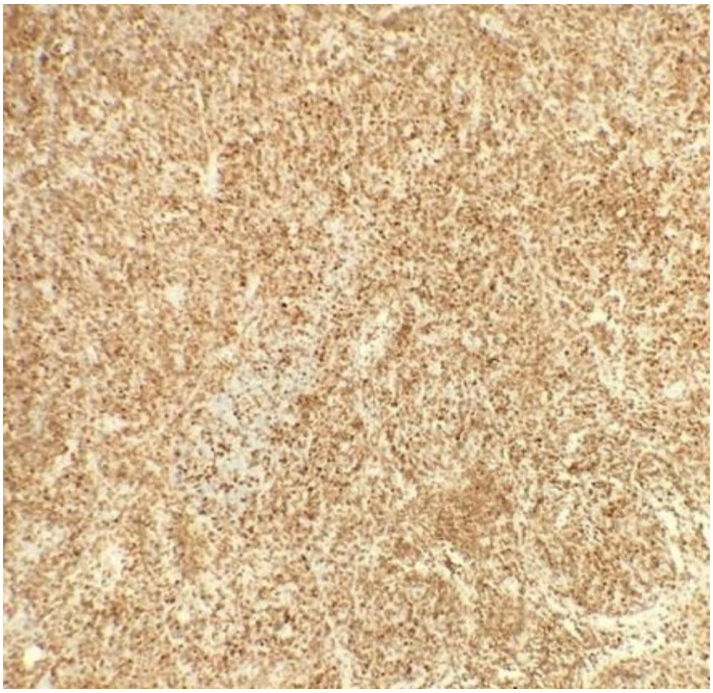

Fig. 3. Immunohistochemistry (IHC) CD4 (x200 magnification).

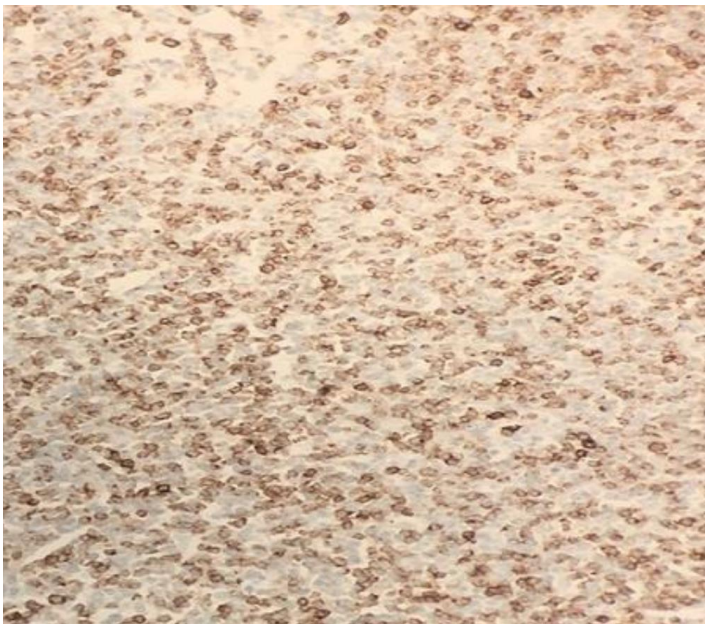

Fig. 4. Immunohistochemistry (IHC) CXCL13 (x200 magnification).

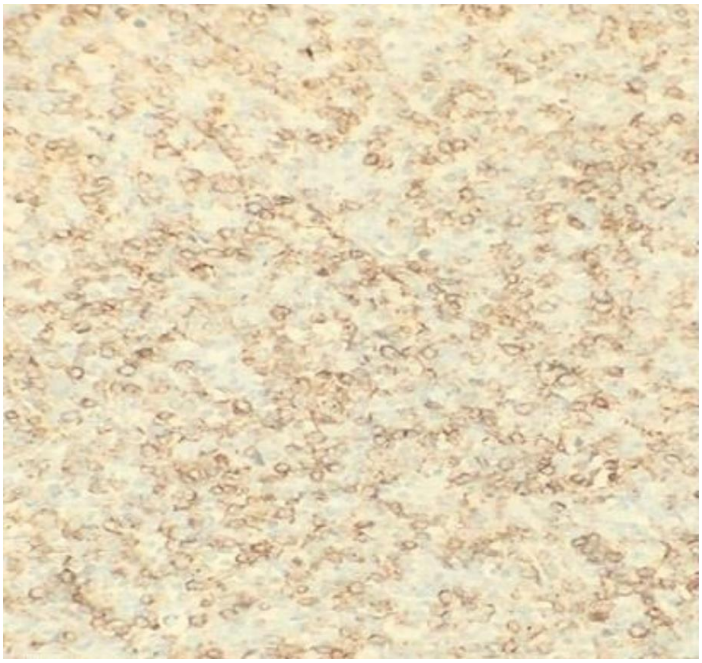

Fig. 5. Immunohistochemistry (IHC) ICOS (x200 magnification).

There were only few remanent follicles comprised by germinal centre B-cells, highlighted by CD20 Figure 6 (CD20 IHC). EBER in-situ hybridization technique showed scattered small positive cells, which appear to co-locate with reactive background B-cells. Figure 7 (EBER ISH).

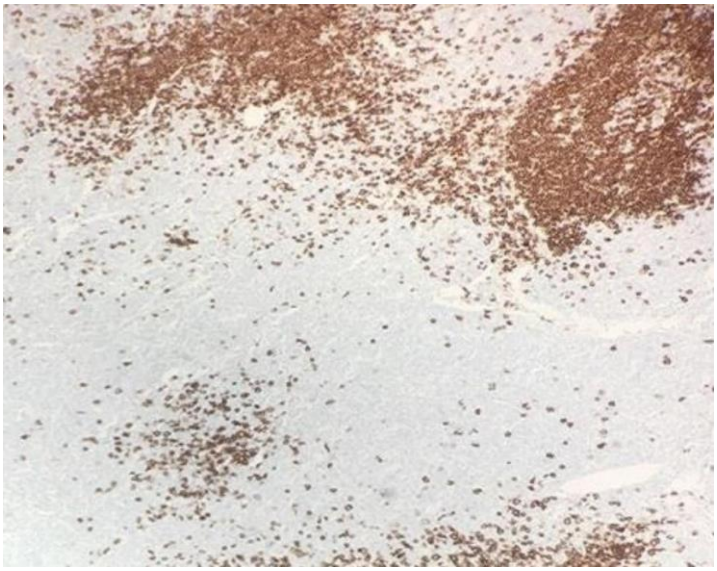

Fig. 6. Immunohistochemistry (IHC) CD20 (x200 magnification).

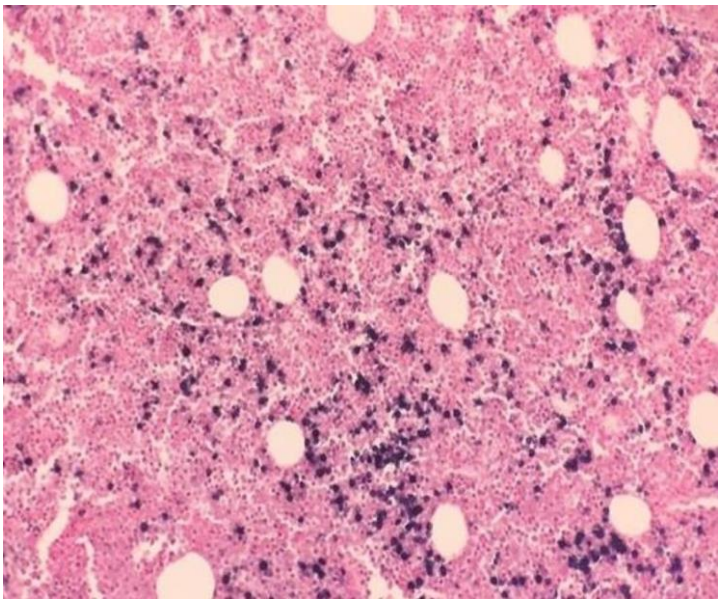

Fig. 7. EBER in situ hybridization. Scattered positivity for EBV RNA material. (x200 magnification).

Molecular studies

Targeted next-generation sequencing (NeoTYPE® AITL/Peripheral T-Cell Lymphoma Profile) identified TET2 c.1648C>T (variant allele frequency [VAF] 26%) and DNMT3A p.G543C (VAF 21%); RHOA G17V and IDH2 R172 variants were not detected. Multiplex PCR confirmed clonal TCR-γ/β rearrangements.

Differential diagnosis

Peripheral T-cell lymphoma, NOS with TFH-like features. Hodgkin lymphoma with aberrant T-cell phenotype. Reactive hyperplasia or immunodysregulation-associated lymphadenitis. Reactive follicular T-cell lymphoma.

Management and outcome

The patient received six cycles of CHOEP, achieving a partial response, followed by consolidative autologous stem-cell transplantation. Twelve months post-transplant he remains in clinical remission (Deauville 3).

DISCUSSION OF THE CASE

Angioimmunoblastic T-cell lymphoma (AITL) poses a unique diagnostic and therapeutic challenge, particularly when canonical T-follicular helper (TFH) markers CD10 and BCL6 are absent. CD10-negative series by Xie, et al. and Attygalle, et al. demonstrated that a broadened TFH panel—PD-1, ICOS, CXCL13—combined with next-generation sequencing (NGS) detection of co-occurring TET2 and DNMT3A mutations, can secure the diagnosis, a concept now codified in the 2022 International Consensus Classification.[5,6]

Genomically, AITL is characterised by early epigenetic lesions (TET2, DNMT3A) that frequently precede acquisition of pathognomonic RHOA G17V or IDH2 R172 mutations. These mutations arise in haematopoietic stem cells, explaining the co-presence of identical variants in non-tumor myeloid or B-cell compartments and the association with clonal haematopoiesis. Epstein-Barr virus–positive immunoblasts, observed in roughly one-third of cases, further accentuate polymorphous histology, but have limited prognostic impact.

Prognostically, AITL remains one of the most aggressive mature T-cell lymphomas. CHOP-like regimens confer a median overall survival (OS) of 24–36 months and a 5-year OS of 25% –35%.[4] The CHOEP modification yields incremental benefit in younger, fit patients, while dose-intensive therapy followed by upfront autologous stem-cell transplantation (ASCT) can elevate 3-year progression-free survival (PFS) to approximately 54% and OS to approximately 71%.[7] Allogeneic transplantation represents the only potentially curative approach in relapsed/refractory disease, albeit with 20% – 30% treatment-related mortality.[8,9]

The therapeutic landscape is rapidly evolving. Histone deacetylase inhibitors (romidepsin, belinostat, chidamide) and the hypomethylating agent oral azacitidine—alone or with lenalidomide—achieve overall response rates (ORR) of 30% – 45%, with durable responses particularly in epigenetically mutated tumours. PI3Kδ/γ inhibition (duvelisib) has produced a 2-year PFS exceeding 60% in TFH-phenotype lymphomas, and the ECHELON-2 trial established brentuximab vedotin plus CHP as a frontline standard for CD30-positive peripheral T-cell lymphoma, achieving a 2-year PFS of 63% within the TFH subset.[10] Ongoing studies combining epigenetic agents with checkpoint blockade, CD47 or ICOS antagonists, and next-generation PI3K inhibitors aim to deepen and prolong remissions.

In this rapidly shifting milieu, we advocate a risk-adapted strategy encompassing early ASCT consolidation for eligible patients and prompt enrolment onto clinical trials evaluating novel biologics. Routine NGS not only refines classification but will increasingly guide precision therapy as mutation-specific agents emerge.

FINAL CONSIDERATIONS

AITL lacking CD10/BCL6 can be confidently diagnosed through expanded TFH immunohistochemistry and mutation profiling. Early molecular characterization not only increases diagnostic certainty but may also inform the use of emerging targeted therapies.

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Conflict of interest:
The authors declare that they have no conflict of interest.

Author contributions:
Alvaro Frometa: conceptualization, formal analysis, investigation, methodology, resources, supervision, writing-original draft, writing-revision and editing.
Robert W. Allan: investigation, methodology, writing-original draft, writing-revision and editing.
Yasna Chaudary: formal analysis, writing-original draft, writing-revision and editing.

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