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CASE REPORT

Dermatomyositis Resolution after Neoadjuvant Therapy in HER2 Positive Breast Cancer: A Case Study

CRISTINA ELENA BIȚĂ[1)], BOGDAN IONEL VĂTU[2)], ANDREEA CRISTINA MANAFU[3)], ȘTEFAN CRISTIAN DINESCU[1)], SINETA CRISTINA FIRULESCU[3)], BEATRICE ANDREEA TRAȘCĂ[4)], ANDREEA LILI BĂRBULESCU[5)], FLORENTIN ANANU VREJU[1)]

[1)]Department of Rheumatology, University of Medicine and Pharmacy of Craiova, Romania
[2)]Department of Oncology, Emergency County Hospital Craiova, Romania
[3)]Department of Rheumatology, Emergency County Hospital Craiova, Romania
[4)]Medical Center Ecomed Research Craiova, Romania
[5)]Department of Pharmacology, University of Medicine and Pharmacy of Craiova, Romania

Abstract

Background. Dermatomyositis (DM) is a rare disease that belongs to the idiopathic inflammatory myopathies, and is characterized by inflammation and weakness of proximal skeletal muscles, accompanied by skin rash.
Furthermore, DM can manifest clinically as a paraneoplastic syndrome in patients with breast cancer. Managing the progression of DM is typically achievable with elevated doses of glucocorticoids in the majority of cases. Nonetheless, when faced with a severe manifestation of the paraneoplastic syndrome, initiation of cancer treatment is imperative.
Methods. We report a clinical case of 34-year-old female, presenting heliotrope rash and Gottron's papules. In addition, there was a development of severe proximal muscle weakness with severe dysphagia and dysphonia. The clinical features and laboratory results led to the diagnosis of DM. Concomitantly, the patient was diagnosed with a stage IV M1 HEP, HER2 positive breast neoplasm.
Results. At first, high dose of glucocorticosteroids was administered as pulse therapy due to the severe symptoms of the paraneoplastic syndrome. Then anti-HER molecular targeted-therapy and chemotherapy were applied, as well as oral glucocorticoids for DM control. The patient showed significant improvement following three months of treatment, both in clinical and biological aspects.
Conclusion. This case report underscores the importance of recognizing dermatomyositis in adults as a paraneoplastic syndrome associated with underlying malignancies.

Keywords: paraneoplastic dermatomyositis, breast cancer, idiopathic inflammatory myopathy, autoantibodies.

Introduction

Dermatomyositis (DM) and polymyositis are categorized within a heterogeneous group known as idiopathic inflammatory myopathies (IIMs), which are disorders affecting connective tissue. DM is a rare condition, primarily identified as an IMM driven by complement activation, characterized by specific skin rashes and muscle weakness in the in the proximal muscles [1].

Reports indicate that DM occurs at a rate of 0.5 to 0.89 cases per 100 000 individuals annually, with a higher prevalence in middle-aged women, who are affected twice as often as men in the same age group [2]. While often considered idiopathic, there has been a considerable amount of medical literature dating back to 1916 that associates myopathies with various malignancies [3].

Further studies have elucidated the increased risk of malignancies in patients with DM, as evidenced through comprehensive retrospective case reviews and population-wide studies. A correlation between DM and malignancy was found in approximately 24% of the cases [4]. A wide variety of cancers have been linked to DM, with the specific types observed differing significantly according to the patient's ethnicity.

Consequently, the spectrum of cancers linked to DM reflects those commonly found in the general population, including ovarian, lung, gastrointestinal, breast, and non-Hodgkin lymphomas as some of the most frequently associated cancers [5,6]. Paraneoplastic DM can manifest prior to, concurrently with, or after the identification of a neoplastic condition [7].

The pathogenesis of paraneoplastic DM is characterized by complex immune reactions, in which the immune system's defense against a tumor cross-reacts with skin and muscle cells. This overlap in immune

response leads to the symptoms and clinical manifestations seen in DM.

The aim of this case presentation is to highlight that, widespread conditions, such as breast cancer, can present through atypical signs like DM as a paraneoplastic syndrome. Therefore, it's essential for healthcare professionals to consider the possibility of an underlying neoplasia when diagnosing DM in adult patients.

Case report

A 35-year-old female patient was referred to the emergency department of the Craiova County Clinical Hospital with symmetrical polyarthralgia in the small joints of the hands, elbows and knees, myalgia of increased intensity, accompanied by significant muscle weakness in the scapular and pelvic girdles with impossibility of movement. The patient has a history of hormonal treatments with oral contraceptives and four natural births with physiological lactation. The hereditary history is not significant.

The patient was admitted to the Internal Medicine department. The initial assessment revealed also involvement of the flexor muscles of the neck with impossibility of lifting the head from the pillow, intermittent dysphagia for solids and liquids, as well as the presence of dysphonia. In addition, about a month ago, the patient reports the appearance of a heliotrope rash, accompanied by bilateral marked palpebral edema, and an erythematous rash located on the face (Figure 1), upper anterior chest region, neck, shoulders, upper and lower limbs. On the extensor aspect of the metacarpophalangeal and interphalangeal joints there were erythematous papules with a discrete psoriatic appearance, suggestive of Gottron's papules, and telangiectasias at the periungual level (Figure 2).

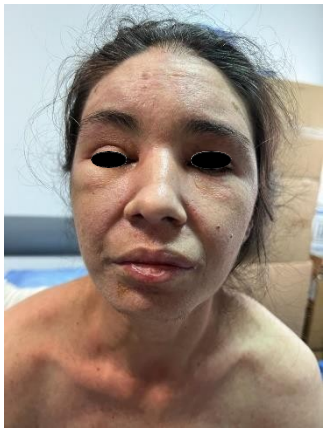

Figure 1 – Heliotrope rash, marked by violet discoloration on the eyelids, accompanied by bilateral pronounced palpebral edema.

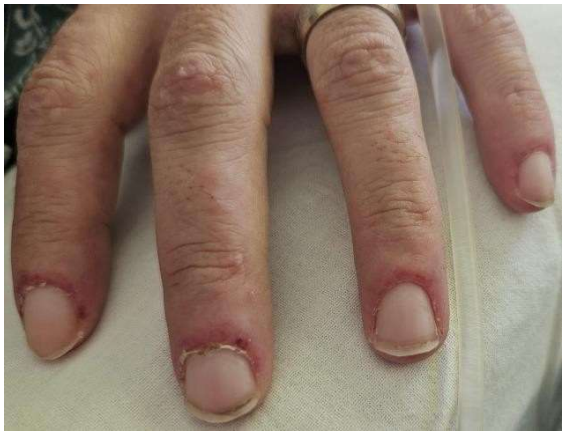

Figure 2 – Gottron's papules, distinctive erythematous papules overlying the interphalangeal joints, along with periungual telangiectasias.

During the clinical breast examination, an area of nodularity was detected in the upper outer quadrant of the left breast, suggestive for of invasive malignancy. Additionally, a solitary large, movable pathological lymph node was found in the left axilla.

To evaluate the breast lesion, the patient underwent both mammary ultrasound and mammography. The tests revealed a solid, hypoechoic, vascularized lesion with irregularly lobulated contours and some microcalcifications, measuring at least 40 mm, located in the left external mammary quadrants. Additionally, suspected lymphadenopathies were observed in the ipsilateral axillary region, with the largest measuring 14 mm. Once the breast tumor incisional biopsy was performed, the patient was diagnosed with infiltrating ductal carcinoma, grade 4, HER2-positive and Ki67 22%. Also, the computed tomography revealed the presence of liver metastases.

The patient was subsequently transferred to the Rheumatology Clinic with degradation of the general condition due to the exacerbation of the symptoms present on admission: fever, weight loss marked by total dysphagia, dysphonia, functional impotence of the lower and upper limbs, as well as an increase in the intensity of myalgia.

We performed a periungual capillaroscopy which revealed changes suggestive for DM, precisely marked architectural disorganization, loss of capillary loops, frequent dilated capillaries and microhemorrhages, megacapillaries, and arborescent capillaries (Figure 3).

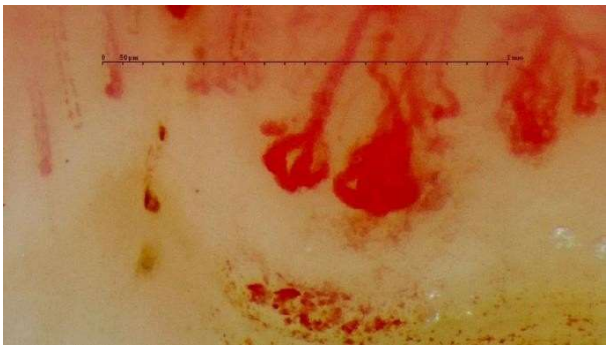

Figure 3 – Capillaroscopy image illustrating architectural disorganization, loss of capillary loops, presence of megacapillaries, microhemorrhages, and arborescent capillaries, suggestive of microvascular abnormalities in the context of DM.

The laboratory tests showed creatine kinase (CK) of 8048 U/L, aspartate aminotransferase of 367 U/L, alanine aminotransferase of 241 U/L and lactate dehydrogenase of 1292 U/L. Electromyography (EMG) revealed myopathic abnormalities in the proximal muscles of the upper limbs, characterized by the presence of fibrillation potentials and positive sharp waves. Moreover, presence of anti-nuclear antibodies (1:160, speckled), anti TIF1 and anti-Ro52 (SS-A)-antibodies were detected.

Following clinical manifestations (proximal muscle weakness in the scapular and pelvic girdles, involvement of neck flexor muscles, dysphagia and dysphonia), paraclinical examinations (increased levels of muscle and liver enzymes with predominance of aspartate aminotransferase), myopathic changes on EMG, and skin manifestations (heliotropic rash, periorbital oedema, shawl sign, V-shaped erythema and Gottron's papules), the patient met Bohan and Peter's diagnostic criteria for DM. Thus, suspicion of paraneoplastic DM, associated with a stage IV M1 HEP, HER2 positive breast neoplasm was formulated.

It is widely recognized that CK can be harmful to the kidneys. Therefore, in order to prevent acute kidney damage, the patient was administered a large volume of intravenous 0.9% saline solution to achieve a urine output of 300 ml/h or higher. Additionally, a 5% dextrose solution with sodium bicarbonate was provided to mitigate urine acidosis. A high dose of corticosteroids was administered as pulse therapy, consisting of methylprednisolone at a dosage of 1 g per day for three consecutive days. After the first dose of pulse therapy, the patient related a modest improvement in muscle symptoms, and we registered favorable response of inflammatory markers and muscle enzymes.

Taking into account the paraneoplastic etiology of the DM, the patient was referred to the medical oncology team. After hydroelectrolytic equilibration and the assembly of a percutaneous endoscopic gastrostomy tube to maintain nutrition, specific treatment for oncological pathology was initiated with double anti-HER2 blockade (trastuzumab+pertuzumab) and chemotherapy with docetaxel for 21 days. Also, a dosage of 25 mg/day of prednisone was maintained for the DM control.

The patient tolerates with difficulty the first cytostatic dose and develops febrile neutropenia and bilateral basilar pneumonia remitted under wide spectrum antibiotic treatment. She is subsequently discharged and presents for cycle two of oncology-specific treatment with normal muscle enzyme and inflammatory marker values and significant improvement in clinical manifestations, resuming oral alimentation and partial mobilization concomitant with complete remission of eyelid edema and rash.

Discussion

DM, categorized as an IIM subtype, is characterized by a progressive development of skin abnormalities, muscle weakness, and specific features observed in muscle biopsies. While its primary impact is on the muscles and skin, it can also involve the heart, lungs and joints [9]. Hallmark characteristics of DM include the presence of Gottron's papules and a purplish-red rash encircling the eyes, referred to as a heliotrope rash. Additional skin manifestations might include holster sign, poikiloderma, calcinosis cutis, skin changes resembling psoriasis, and erythroderma [10,11]. The etiology of DM is thought to result from a blend of genetic predisposition, environmental influences, and dysregulation in immune system function.

The diagnosis of DM is established using Bohan and Peter's 1975 criteria, encompassing clinical symptoms, EMG results, elevated levels of muscle enzymes, and findings from muscle biopsies [12]. The differentiation between idiopathic DM and DM related to neoplasia primarily lies in the potential for resolution or improvement by treating the underlying malignancy.

Paraneoplastic DM is a subtype of DM occurring as part of a paraneoplastic syndrome, highlighting its association with an underlying cancer. Approximately 15% to 30% of DM cases are linked to cancer-associated myositis [13]. When DM is identified in individuals aged 45 or older, it warrants a comprehensive oncological evaluation [14]. DM frequently associates with malignancies such as lung, ovarian, stomach, pancreatic, colorectal cancers, and non-Hodgkin lymphoma. Among females, there is a 20% correlation with breast cancer. [15]. The most prevalent histological type observed is ductal carcinoma, with no statistical patterns found regarding hormone receptor status and HER2 positivity [16]. Symptoms may manifest prior to, simultaneously with, or following the diagnosis of breast cancer, and their recurrence could indicate a relapse [16].

Although the exact etiology of cancer-associated myositis remains unclear, there are many proposed theories to explain the above condition. Some of them include: the paraneoplastic nature of DM through tumor-produced mediators, shared environmental factors which induced autoimmune reactions or malignant transformation triggered by agents for DM management [17].

The pathogenesis of DM is not fully understood and several mechanisms have been suggested. Immune complexes accumulate at the skin-muscle junction, accompanied by an increase in CD4 T cells and B

lymphocytes, mainly in the perivascular regions. Features like capillary loss, blood clot formation, and damage to blood vessel walls are key indicators of DM. A theory linking DM to cancer suggests that tumor cells might emit proteins that trigger an immune response, leading to the accumulation of auto-antibodies in the muscles and skin where similar antigens are found [18].

Studies have shown that specific autoantibodies linked to myositis correlate with distinct clinical signs. High levels of anti-TIF-1γ and anti-NXP2, often seen in about 80% of paraneoplastic cases, are usually associated with severe skin manifestations and difficulty swallowing. Furthermore, a recent meta-analysis indicated that individuals with elevated anti-TIF-1γ levels are significantly more likely to develop malignancy, with a 27 times higher odds ratio [19,20]. Moreover, TIF-1 family proteins, such as TIF-1γ and TIF-1α, play roles in pathways related to tissue differentiation, cell proliferation, apoptosis or innate immunity [21].

Breast cancer, affecting countless women globally, is a heterogeneous and intricate disease. Notably, the human epidermal growth factor receptor 2 (HER2)-positive subtype is recognized for its aggressive nature. The HER2 is crucial in breast cancer prognosis, serving as both a negative indicator and a therapeutic target, remarkably for trastuzumab and other anti-HER2 agents. To determine HER2 status, diagnostic pathology commonly employs immunohistochemistry (IHC) for measuring HER2 protein levels and in situ hybridization (ISH) for analyzing HER2 gene status.

The HER2 is a member of the Human Epidermal Receptor family, functioning as an orphan tyrosine kinase receptor without a specific ligand. It readily pairs with the family's other receptors, initiating signaling pathways that enhance cell growth, movement, and survival upon dimerization. Around 15% of breast cancers show HER2 overexpression due to amplification, which, while linked to poor outcomes, also allows for targeted therapy with trastuzumab, a monoclonal antibody that disrupts HER2's signaling by targeting its external domain [22].

Furthermore, for patients with HER2-positive disease, there's evidence indicating that trastuzumab may also play a role in inhibiting the paraneoplastic process [23]. This hypothesis is supported by the presented case, suggesting that neoadjuvant chemotherapy is not only effective for remitting symptoms in cases of HER2 positivity, but also in cases of paraneoplastic dermatomyositis.

The primary approach to treating DM typically involves corticosteroids and immunosuppressant agents, with immunoglobulins used as a secondary option. Additionally, addressing the neoplasia in these patients often results in improvement of the myositis [24]. Remission in DM has been linked to surgical removal aimed at treating the condition and immunosuppressive therapy, although outcomes vary. It has additionally been noted that myopathy can recur with the recurrence of malignancy, further reinforcing the idea of a paraneoplastic origin for malignancy-associated DM [16,25]. This implies that the clinical monitoring of patients previously diagnosed with malignancy-associated DM should involve vigilance for signs of recurrent malignancy, along with symptoms and indications of recurring myopathy.

Conclusion

To summarize, despite DM being a rare autoimmune condition typically emerging as an idiopathic disease, identifying DM in an adult should lead to an evaluation for potential underlying malignancy. It is also important to note that DM associated with an underlying cancer can appear either simultaneously with or at a different time from the cancer diagnosis, often with an average interval of 2 years.

Therefore, DM can also present as a clinical sign of a paraneoplastic syndrome in individuals with breast cancer. It remains an uncommon diagnosis, with limited evidence available to guide treatment strategies to date. Controlling the progression of DM is achievable through the use of high doses of glucocorticoids along with immunosuppressive agents, while addressing the cancer through prompt surgical intervention is recommended. The resolution of the paraneoplastic syndrome often follows the removal of the cancer. Additionally, employing neoadjuvant chemotherapy, particularly when warranted and in association with paraneoplastic dermatomyositis, can prove beneficial. However, additional data are needed to determine the optimal management strategies for these patients in order to achieve significantly prolonged survival.

References

[1] Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet, 2003, 362 (9388):971-982. https://doi.org/10.1016/S0140-6736(03)14368-1.

[2] Christie A, McKay N, Nussey F. Dermatomyositis as presenting feature of ovarian cancer, treated with neo-adjuvant chemotherapy and interval debulking surgery. Gynecol Oncol Case Reports, 2013, 6:13-15. https://doi.org/10.1016/j.gynor.2013.07.002.

[3] Ungprasert P, Leeaphorn N, Hosiriluck N, Chaiwatcharayut W, Ammannagari N, Raddatz DA. Clinical Features of Inflammatory Myopathies and Their Association with Malignancy: A Systematic Review in Asian Population. ISRN Rheumatol 2013, 2013:1-7. https://doi.org/10.1155/2013/509354.

[4] Zahr ZA, Baer AN. Malignancy in Myositis. Curr Rheumatol Rep 2011, 13:208–215. https://doi.org/10.1007/s11926-011-0169-7.

[5] Zerdes I, Tolia M, Nikolaou M, Tsoukalas N, Velentza L, Hajiioannou J, Mitsis M, Kyrgias G. How can we effectively address the paraneoplastic dermatomyositis: Diagnosis, risk factors and treatment options. J BUON 2017, 22(4):1073-1080. PMID: 28952230.

[6] Nikolaos T, Maria T, Ioannis KD, Georgios L, Nikolaos P, Stamatina D, Christos P, Georgios K, Vasileios B, Anna E. Dermatomyositis as an early manifestation and a significant clinical precursor of lung cancer: report of a rare case and review of the current literature. Int J Clin Exp Med 2013, 6(2):105-109. PMID: 23386913.

[7] Femia AN, Vleugels RA, Callen JP. Cutaneous Dermatomyositis: An Updated Review of Treatment Options and Internal Associations. Am J Clin Dermatol 2013, 14(4):291-313. https://doi.org/10.1007/s40257-013-0028-6.

[8] Scharman EJ, Troutman WG. Prevention of Kidney Injury Following Rhabdomyolysis: A Systematic Review. Ann

Pharmacother 2013, 47(1):90-105. https://doi.org/10.1345/aph.1R215.
[9] Piras M, Panebianco M, Garibaldi M, Roberto M, Merlonghi G, Pellegrini P, Marchetti P. A Case of Pathological Complete Response and Resolution of Dermatomyositis Following Neoadjuvant Chemotherapy in HER2-Positive Early Breast Cancer. Curr Oncol 2021, 28(3):1957-1961. https://doi.org/10.3390/curroncol28030182.
[10] Ahuja S, Makkar P, Gupta S, Vigoda I. Paraneoplastic syndrome and underlying breast cancer: a worsening rash despite initiation of chemotherapy. J Community Support Oncol 2016, 14(5):229-231. https://doi.org/10.12788/jcso.0186.
[11] Levine TD. History of Dermatomyositis. Arch Neurol 2003, 60(5):780-782. https://doi.org/10.1001/archneur.60.5.780.
[12] Chakroun A, Guigay J, Lusinchi A, Marandas P, Janot F, Hartl DM. Paraneoplastic dermatomyositis accompanying nasopharyngeal carcinoma: Diagnosis, treatment and prognosis. Eur Ann Otorhinolaryngol Head Neck Dis 2011, 128(3):127-131. https://doi.org/10.1016/j.anorl.2010.10.007.
[13] Ikeda N, Yamaguchi Y, Kanaoka M, Ototake Y, Akita A, Watanabe T, Aihara M. Clinical significance of serum levels of anti-transcriptional intermediary factor 1-γ antibody in patients with dermatomyositis. J Dermatol 2020, 47(5):490-496. https://doi.org/10.1111/1346-8138.15284.
[14] Luu X, Leonard S, Joseph K-A. Dermatomyositis presenting as a paraneoplastic syndrome with resolution of symptoms following surgical management of underlying breast malignancy. J Surg Case Reports 2015, 2015(7):rjv075. https://doi.org/10.1093/jscr/rjv075.
[15] Levine SM. Cancer and myositis: new insights into an old association. Curr Opin Rheumatol 2006, 18(6):620-624. https://doi.org/10.1097/01.bor.0000245721.02512.77.
[16] Osako T, Ito Y, Morimatsu A, Tada K, Sakurai N, Takahashi S, Akiyama F, Iwase T, Hatake K. Flare-up of Dermatomyositis Along with Recurrence of Breast Cancer. Breast J 2007, 13(2):200-202. https://doi.org/10.1111/j.1524-4741.2007.00400.x.
[17] Naschitz JE, Rosner I, Rozenbaum M, Zuckerman E, Yeshurun D. Rheumatic syndromes: Clues to occult neoplasia. Semin Arthritis Rheum 1999, 29(1):43-55. https://doi.org/10.1016/S0049-0172(99)80037-7.
[18] Kissel JT, Mendell JR, Rammohan KW. Microvascular Deposition of Complement Membrane Attack Complex in Dermatomyositis. N Engl J Med 1986, 314(6):329-334. https://doi.org/10.1056/NEJM198602063140601.
[19] Trallero-Araguás E, Rodrigo-Pendás JÁ, Selva-O'Callaghan A, Martínez-Gómez X, Bosch X, Labrador-Horrillo M, Grau-Junyent JM, Vilardell-Tarrés M. Usefulness of anti-p155 autoantibody for diagnosing cancer-associated dermatomyositis: A systematic review and meta-analysis. Arthritis Rheum 2012, 64(2):523-532. https://doi.org/10.1002/art.33379.
[20] Kubeček O, Soukup T, Paulík A, Kopecký J. Dermatomyositis with anti-TIF-1γ antibodies as a presenting symptom of underlying triple-negative breast cancer: a case report. BMC Cancer 2016, 16:684. https://doi.org/10.1186/s12885-016-2715-1.
[21] Maier L, Betteridge Z, Udvardi A, Schmid-Simbeck M, Seeber A, Volc-Platzer B. Paraneoplastic Dermatomyositis: relevance of myositis-specific autoantibodies in a small cohort. J Eur Acad Dermatology Venereol 2020, 34(2):e50-e51. https://doi.org/10.1111/jdv.15897.
[22] Sapino A, Goia M, Recupero D, Marchiò C. Current Challenges for HER2 Testing in Diagnostic Pathology: State of the Art and Controversial Issues. Front Oncol 2013, 3:129. https://doi.org/10.3389/fonc.2013.00129.
[23] Pellegrino B, Mazzaschi G, Madeddu D, Mori C, Lagrasta CAM, Missale G, Quaini F, Musolino A. Clinico-Immunological Profile of a 67-Year-Old Woman Affected by HER2-Positive Breast Cancer and Autoimmune Dermatomyositis. Front Oncol 2020, 10:192. https://doi.org/10.3389/fonc.2020.00192.
[24] Lamquami S, Errarhay S, Mamouni N, Bouchikhi C, Banani A. Dermatomyositis revealing breast cancer: report of a case. Pan Afr Med J 2015, 21(89). https://doi.org/10.11604/pamj.2015.21.89.6971.
[25] Voravud N, Dimopoulos M, Hortobagyi G, Ross M, Theriault R. Breast cancer and second primary ovarian cancer in dermatomyositis. Gynecol Oncol 1991, 43(3):286-290. https://doi.org/10.1016/0090-8258(91)90037-6.

Corresponding author
Ștefan Cristian Dinescu, Department of Rheumatology, University of Medicine and Pharmacy Craiova, 2 Petru Rareş Street, 200349 Craiova, Romania; Phone, e-mail: dinescu.stef@gmail.com

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