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Can we clinically identify patients at risk of malignant transformation of skin tumors in Brooke–Spiegler syndrome?

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Abstract

Brooke–Spiegler syndrome (BSS) is a rare inherited autosomal dominant disease characterized by the development of multiple adnexal cutaneous neoplasms. BSS has been linked to mutations in *CYLD* gene, which is a tumor suppressor gene located on chromosome 16q12-q13. An increased risk of malignant transformation of adnexal cutaneous tumors in BSS patients has been reported. However, no reported genetic markers identify patients at risk of cutaneous malignancy. This study reviews published cases of BSS to investigate the role of clinical parameters as biomarkers of skin malignancy. A comprehensive review of the clinical aspects of BSS is based on 55 case reports. Our analysis revealed only age as a predictor of malignancy; however, this is also a general risk factor for development of malignancy and therefore of limited value as a screening tool. The study highlights the need for standardized clinical follow-up of patients.

Keywords: Brooke–Spiegler syndrome, malignancy, predictors, genetics

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Introduction

Brooke–Spiegler syndrome (BSS) is a rare inherited autosomal dominant disease characterized by the development of multiple adnexal cutaneous neoplasms including cylindromas, trichoepitheliomas, spiradenocylindromas, and spiradenomas. It was first described by Ancell in 1842 (1–4). In 1929, Wiedemann described a malignant cylindrocarcinoma characterized by loss of the typical "jigsaw pattern" and of the peripheral palisading of the basaloid cells (polymorphous clear cells with prominent nucleoli) (5).

Although congenital, BSS typically becomes clinically apparent in adolescence or early adulthood with cylindromas, trichoepitheliomas, and/or less commonly spiradenomas. The diagnosis is mainly based on clinical examination, although dermoscopy may help in the clinical differentiation from other skin tumors (6, 7). Most nodules are in the range of 0.5 to 3 cm in diameter, but larger lesions can be seen.

BSS presents a wide spectrum with multiple familial trichoepitheliomas (MFT) and familial cylindromatosis (FC) at either end. Both are allelic diseases with a common genetic basis (2). Whereas FC is categorized by cylindromas, MFT is described by the development of numerous trichoepitheliomas without accompanying cylindromas, spiradenomas, or spiradenocylindromas (1). Tumors included in the spectrum of this syndrome are usually benign, but an increased risk of malignant transformation of the adnexal cutaneous tumors in BSS patients has been reported. Both malignant and benign tumors may lead to disfigurement that may independently contribute to depression or other psychological problems (4). Furthermore, patients are reportedly also at increased risk of developing morphologically similar neoplasms in other organs.

BSS has been linked to *CYLD* mutations. Wild-type *CYLD* is a deubiquitinase and tumor suppressor that downregulates the transcription factor NF-κB (8). Mutation of *CYLD* increases resistance to apoptosis, leading to uncontrolled cell proliferation. So far, 93 mutations have been described in the literature. No correlation between location or type of mutation and its phenotypic expression has yet been found (9). This review systematically investigates the clinical parameters of published cases as possible biomarkers of the risk malignant transformation of adnexal cutaneous tumors.

Material and methods

A total of 240 articles were identified through databases—PubMed, MEDLINE (Medical Subject Headings, MeSH), and Embase—using the following search string *(Brooke Spiegler syndrome AND malignancy NOT review[Publication Type]) AND English[lang])*. English-language articles that included patients with BBS and a malignant neoplasm/transformation with architectural and/or cytologic and/or histologic atypia were included. TS screened all titles and abstracts for inclusion, and the 32 cases that met the selection criteria mentioned above form the basis of this study.
In order to identify a control group with BSS without malignancy, a second search using the following terms was made (March 15th, 2018): ("Familial cylindromatosis"[Supplementary Concept] OR "Familial cylindromatosis"[All Fields] OR "Brooke Spiegler syndrome"[AllFields])NOT("review"[PublicationType]OR"review

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literature as topic"[MeSH Terms] OR "review"[All Fields]) AND English[lang]. Eighteen articles containing a total of 23 cases were identified.

Results

Clinical data

Table 1 shows the essential clinical data of 32 patients with BSS with malignancy compiled from 28 publications. Table 2 shows the data from 23 cases (one report with eight cases) with BSS and without malignancy, and Table 3 compares the general clinical findings in the two groups.

The malignant elements did not present a homogenous clinical picture, and the family histories disclosed similar lesions involving relatives of 18 patients (cases 1–3, 6, 7, 9, 10, 13, 16, 19, 20, 25, and 28–32). However, it is unknown whether these lesions were benign or malignant, or BSS-related. Five individuals with histopathologically confirmed basal cell carcinoma (BCC) (three females and two males) presented with multiple groups of confluent nodules or tumors ranging in size from 0.5 to 10 cm. In some cases, the initial presentation of the tumors in early adolescence was clinically classified as benign; however, they transformed into rapidly growing bleeding or ulcerating tumors between the ages of 46 and 68 (malignancy subsequently confirmed by histopathology).

Information on follow-up after surgical excision was available for 37.5% (12/32) patients. The follow-up time from 6 to 144 months revealed recurrence in six of the 12 cases.

Case descriptions of non-malignant BSS patients were also found (Table 2).

In the population with BSS without the development of malignancy, the average tumor size was described in three cases. The size varied from 0.2 to 4 cm. Otherwise, the descriptions did not obviously differ from those of the malignant tumors.

Genetic analysis

In the population with BSS and development of malignancy, information on family history was available in 11 cases. From these cases genetic analysis was only available for five cases and re-

Table 1 | **Brooke–Spiegler syndrome with malignancy.**

Case number (reference)	Sex/ age	Clinical aspects (size etc.)	Location	Malignancy confirmed by histopathology	Other benign tumors confirmed by histopathology	Mutation	Family history
1 (18)	F/48	Multiple soft tumors of the scalp	Scalp	Non-Hodgkin lymphoma	Cylindroma	*CYLD* gene heterozygosity for a c.2465insAACA mutation in exon 17	History with similar cases among living relatives
2 (19)	F/57	Multiple, discrete, confluent nodules	Scalp, ears, central face, trunk, limbs	BCC × 8	Cylindromas, trichoblastomas, trichoepitheliomas, spiradenomas	Heterozygous missense germline mutation in exon 5	Nine clinically affected family members
3 (20)	F/67	Multiple cutaneous nodules; palpable nodule also found in left parotid gland	Scalp, face, posterior thoracic wall, parotid gland	Basal cell adenoma (parotid gland nodule)	Eccrine cylindroma (cheek nodule)	Sequencing of *CYLD* gene revealed novel mutation at c.2042-1G›C in splicing acceptor site of exon 15	History with no similar cases among living relatives
4 (21)	F/46	Facial lesions polymorphic, pale, confluent, skin-colored, papular; scalp lesions erythematous with violet lumps that varied in size	Head, auricles, scalp	BCC	Not mentioned	Not mentioned	Unknown
5 (22)	F/83		Face, scalp, ears	Malignant cylindroma, cylindrocarcinoma	Benign cylindroma, four spiradenomas, four combined cylindromas + spiradenomas	Not mentioned	Unknown
6 (23)	F/55	Numerous painless, round-to-oval, discrete and/or confluent, soft and firm, skin-colored or pinkish papules and nodules ranging from 1 to 5 cm in size; pruritic and ulcerated recently	Face	BCC	Not mentioned	Not mentioned	Patient had six sons and two daughters with skin tumors
7 (24)	F/47	Multiple 0.5 to 2.0 cm pinkish-tan papules on patient's upper back and upper arms	Face	BCC	BCC	Not mentioned	Daughter and mother with similar lesions

Table 1 | **Continued.**

Case number (reference)	Sex/ age	Clinical aspects (size etc.)	Location	Malignancy confirmed by histopathology	Other benign tumors confirmed by histopathology	Mutation	Family history
8 (25)	M/40	Numerous skin-colored papules predominantly on central face, with larger 2.1 × 1.2 × 1 cm pink papule on left side of nose	Nose	Trichoblastic carcinoma	Trichoblastic carcinoma	Not mentioned	No family history
9 (26)	M/58	Multiple scalp and periauricular lesions, one ulcerated	Scalp and periauricular	BCC	BCC arising in contiguity with TE	Heterozygous germline mutation in exon 16 c.2116 2117insATTAG(p. Gly706Aspfsx2)	Mother, maternal aunt, maternal grandmother with similar phenotype
10 (27)	M/46	Multiple discrete and confluent papules and nodules on face, increasing in numbers over the years	Face	BCC	Biopsied material contained 24 TEs, two large nodular BCCs, two spiradenomas, one spiradenocylindroma and one trichoblastoma composed of large and small nodules	*CYLD* mutation c.1684 + 1G>A in exon-intron junction affecting correct splicing with high probability	Patient's mother, grandmother, three brothers, sister, nephew, and one of two sons also affected
11 (28)	F/68	No cutaneous neoplasms	Parotid gland	Spiradenoma with transformation to basal cell adenocarcinoma	Not mentioned	Not mentioned	Unknown
12 (29)	F/58	Numerous firm, rubbery pink tumors on scalp and neck and several nodular lesions on right cheek and upper back; tumor of left parietal area had been ulcerating for several weeks	Scalp	BCC	BCC within cylindroma, cylindroma of scalp, BCC of cheek, TE in nasolabial area	Not mentioned	No family history
13 (30)	F/75	Nodule size from 0.4 to 7 cm, supple, reddish-blue, very numerous, tending to coalesce on scalp; some with smooth surface and others showing erosions, associated with bleeding and foul odor	Scalp, face, and trunk	Carcinosarcoma: biphasic tumor	Biphasic epithelial and sarcomatous features, cylindroma, spiradenoma, TE	Not mentioned	Mother and son had similar skin lesions
14 (31)	M/84	Movable, dermally situated hemispherical 3 cm tumor, said to have existed 4 or 5 years and grown slowly in previous 6 weeks: rapid enlargement, inflammation, and livid discoloration in region	Right forearm	Trichoblastic carcinoma	Not mentioned	Not mentioned	unknown
15 (31)	F/87	Multiple flesh-colored, slowly growing nodules on head, neck, and upper trunk over about 20 years	Head, neck, and upper trunk	BCC	Not mentioned	Not mentioned	Unknown
16 (32)	F/67	Palpable solid, painless lump 1.5 cm in diameter on left periauricular area	Scalp, nasolabial folds, forehead	Parotid gland involvement	Not mentioned	Not mentioned	Daughter with similar lesions over face

Table 1 | **Continued.**

Case number (reference)	Sex/ age	Clinical aspects (size etc.)	Location	Malignancy confirmed by histopathology	Other benign tumors confirmed by histopathology	Mutation	Family history
17 (1)	F/63	3 months: red, rapidly growing tumor on shoulder, arose in preexisting nodular tumor conglomerate present since youth; 7 cm tender, nodular blue and pink tumor conglomerate on right shoulder, in middle of which was 2 cm diameter soft, red- to purple-colored, dome-shaped tumor	Shoulder	Cylindrocarcinoma	Multiple dermal tumors, not connected to epidermis	Not mentioned	Unknown
18 (1)	F/68	Multiple, slowly growing nodular tumors of scalp; 4 months prior patient noticed tender, rapidly growing tumors on scalp; 2 × 3 cm ulcerated soft red tumor	Scalp	Cylindrocarcinoma	Not mentioned	Not mentioned	Unknown
19 (33)	F/68	Multiple large, exophytic nodules situated mostly on scalp and neck, with some lesions on trunk; most lesions on scalp skin-colored with smooth, telangiectatic surface; largest over 10 cm in diameter	Scalp, neck, trunk	Cylindrocarcinoma	Last biopsy obtained from firm and tender tumor mass on neck; histological picture presented morphology of high-grade malignant epithelioid neoplasm	Not mentioned	Son, brother, father, grandmother
20 (34)	F/44	Multiple large, exophytic nodules situated mostly on forehead and scalp; many lesions on ear, some on external ear; most lesions red, firm, covered by teleangiectasies; some seemed cystic	Forehead, scalp, ear	Cylindrocarcinoma	Not mentioned	Not mentioned	Mother and son with similar lesions
21 (25)	M/40	At presentation, nodule on left side of nose growing faster and larger than other TEs; examination revealed numerous skin-colored papules predominantly on central face, with larger 2.1 × 1.2 × 1 cm pink papule on left side of nose	Nose, central face	Trichoblastic carcinoma	Not mentioned	Not mentioned	No
22 (35)	F/59	3.5 cm dome-shaped tumor	Scalp	Trichoblastic carcinoma	Not mentioned	Not mentioned	Unknown
23 (36)	F/35	2-month history of ulcerated, livid 7 × 6.5 × 3 cm mass on sacrum	Os sacrum	Trichoblastic carcinoma	Not mentioned	Not mentioned	Unknown
24 (31)	F/87	Mass on right thigh present about 3 years but had grown rapidly for several weeks; 4 × 4 cm livid mass	Thigh	Trichoblastic carcinoma	Not mentioned	Not mentioned	Unknown
25 (37)	F/56	Ulcerated tumor on dorsum of left hand; tumor on dorsum of hand was pink ulcerated nodule, 20 × 26 mm	Hand	Squamous cell carcinoma	Not mentioned	Not mentioned	Two children, both developed MFT in teens, one confirmed to have pathogenic mutation in *CYLD* (c.1112C>A)

Table 1 | **Continued.**

Case number (reference)	Sex/ age	Clinical aspects (size etc.)	Location	Malignancy confirmed by histopathology	Other benign tumors confirmed by histopathology	Mutation	Family history
26 (38)	M/50	Rapidly enlarging lesion on back; patient first noticed skin tumors around age 18, had multiple lesions removed, confirmed as cylindromas and spiradenomas	Back	Spiradenocarcinoma	Not mentioned	(c.2476C>T; p.Gln823*)	Not mentioned
27 (4)	M/60	Multiple partly confluent tumors on scalp; multiple variably sized red to bluish confluent nodules on scalp; some tumors had grown faster in last 2 years, with largest one (right temporal area) 5 × 3 × 2.5 cm	Scalp	Malignant transformation of spiradenocylindroma salivary gland-type BCAC-HG	Not mentioned	c.2666A>T/p.D889V	Yes
28 (39)	F/66	Large bleeding tumor, 2 cm, on background of smaller multiple tumors; BSS	Back	Salivary gland type BCAC-HG	Not mentioned	Not mentioned	Yes
29 (39)	F/43	Large tumor (6 cm), background of smaller multiple (› 50) tumors; BSS	Neck, upper extremities, chest wall, back, vulva	Salivary gland type BCAC-HG	Not mentioned	Not mentioned	Yes
30 (39)	M/57	Large tumor (3 cm) on background of smaller multiple nodules; BSS	Scalp, face, upper trunk	Salivary gland type BCAC-LG	Not mentioned	Not mentioned	Yes
31 (39)	F/72	Large ulcerated tumor (5 cm) on background of multiple (› 100) small nodules and large tumors, partly grouped, partly ulcerated; BSS	Almost entire integument	Salivary gland type BCAC-LG	Not mentioned	Not mentioned	Yes
32 (39)	F/71	Large tumor (6 × 6.6 × 7 cm) on background of smaller multiple nodules; BSS	Scalp	Salivary gland type BCAC-LG, invasive adenocarcinoma	Not mentioned	Not mentioned	Yes

F = female; M = male; BCC = basal cell carcinoma; BSS = Brooke–Spiegler syndrome; TE = trichoepithelioma; MFT = multiple familial trichoepithelioma; BCAC-HG = basal cell adenocarcinoma-like pattern, high-grade; BCAC-LG = basal cell adenocarcinoma-like pattern, low-grade.

Table 2 | **Brooke–Spiegler syndrome without malignancy.**

Case no. (ref.)	Sex/age	Clinical aspects (size/mm)	Location	Benign tumors confirmed by histopathology	Duration (years)	Family history
1 (40)	F/71	–	Scalp and forehead	Cylindroma	4	+
2 (41)	F/51	–	Small papules on forehead and eyelids	Cylindroma	–	+
3 (42)	F/50	–	Multiple, flesh-colored-to-pink papules and nodules on scalp, face, neck, and upper shoulders	Trichoepithelioma	36	+
4 (43)	M/52	–	Multiple, firm, skin-colored nodules on vertex of scalp	Spiradenoma	–	
5 (44)	F/14	2–4	Dome-shaped, skin-colored, firm papules.	–	–	+
6 (45)	F/70	30–40	Multiple, rounded, smooth-surfaced, firm, non-tender, freely mobile skin-colored to reddish papules and nodules of varying sizes on face (forehead, nose and chin, pre-auricular region, and along jawline)	–	7	–
7 (46)	F/62	–	Numerous soft-tissue lesions of scalp and bilateral preauricular region	–	–	
8 (47)	F/35	2–8	Multiple asymptomatic skin-colored firm papulonodular lesions 2 to 8 mm in diameter, with smooth surface mainly affecting central part of face; scalp showed pinkish, firm, smooth-surfaced, dome-shaped nodules about 1 to 3 cm	Trichoepithelioma	30	+

Table 2 | **Continued.**

Case no. (ref.)	Sex/ age	Clinical aspects (size/mm)	Location	Benign tumors confirmed by histopathology	Duration (years)	Family history
9 (48)	M/30	–	–	Cylindroma	14	
10 (48)	M/32	–	–	Cylindroma	19	
11 (48)	F/19	–	–	Cylindroma	4	
12 (48)	M/8	–	–	Cylindroma	1	
13 (48)	F/48	–	–	Cylindroma	32	
14 (48)	F/29	–	–	Cylindroma	17	
15 (48)	F/65	–	–	Cylindroma	55	
16 (48)	F/38	–	–	Cylindroma	26	
17 (49)	F/46	–	–	–	–	
18 (50)	F/76	–	–	–	–	
19 (51)	F/36	–	–	Trichoepithelioma and cylindroma	–	
20 (52)	F/77	–	Nodular, red, shiny with teleangiectasies, non-ulcerating	–	30	+
21 (53)	F/55	–	–	–	–	+
22 (49)	M/30	–	–	–	–	
23 (54)	F/65	–	–	–	–	+

F = female; M = male.

Table 3 | **Comparison of clinical descriptions of malignant and benign tumors in Brooke–Spiegler syndrome.**

Variable	Malignant	Benign
Age (average & range)	59.5 years (35–87 years)	46 years (8–77 years)
Sex	Women (75%, 24/32)	Women (78%, 18/23)
Duration	Recent rapid growth specifically noted in four cases, but more precise estimate generally unreported	Average 23 years (n = 13)
Distribution	Scalp (50%, 16/32), face (34%, 11/32), ears (9%, 3/32), chest wall (6%, 2/32), shoulder (3%, 1/32), neck (12.5%, 4/32)	Scalp (22%, 5/23), face (13%, 3/23), forehead (17%, 4/23), shoulders (4%, 1/23), neck (4%, 1/23)
Clinical characteristics	0.5 to 10 cm; bleeding mentioned in two cases	0.2 to 4 cm (n = 3)
Description	Polymorphic (1 case), multiple (17), soft (4), ulcerating (4), discrete (3), round (1), pale (1), skin-colored (5), red (6), movable (1)	Multiple (8 cases), soft (1), round (2), skin-colored (7), red (1)

Table 4 | **Mutations in patients with Brooke–Spiegler syndrome.**

Case no. (reference)	Sex/age	Mutation in *CYLD* gene
1 (18)	Female/48	Heterozygosity for c.2465insAACA mutation in exon 17
2 (19)	Female/57	Heterozygous missense germline mutation in exon 5 (no further data available)
3 (20)	Female/67	nt. c.2042-1G>C in splicing acceptor site of exon 15
4 (26)	Male/58	Heterozygous germline mutation in exon 16 c.2116 2117insATTAG(p.Gly706Aspfsx2)
5 (27)	Male/46	c.1684 + 1G>A in exon-intron junction affecting correct splicing with high probability

vealed the presence of BSS in all seven families; the mutations are listed in Table 4 (6, 7). In the population with BSS without malignancy, information on family history was available in eight cases. Unfortunately, there are no data on genetic analysis.

Discussion

BSS is reportedly associated with malignancy, but the clinical characteristics of the association are not well described. To date, no genetic marker of increased risk of malignancy has been identified. We have therefore systematically reviewed the clinical aspects of BSS in 55 case reports and sought to identify clinical characteristics of patients with BSS that developed skin cancer in comparison to BSS patients that did not.

In general, patients in whom malignant transformation was reported were older. The size of both the malignant and benign tumors varied considerably; however, the malignant tumors tended to be larger than the nonmalignant ones. Our review therefore supports the theory that malignant tumors are characterized by classic symptoms such as pain, ulceration, bleeding, discoloration, and rapid growth (5, 10–12). The review of published cases does not support the previous suggestions that the total tumor mass as reflected by multiple cylindromas also constitutes an independent risk factor (1).

Textbooks and review articles often mention a risk of progression from benign to malignant skin tumors. Transformation into spiradenoma has been reported with carcinomatous or sarcomatous differentiation, but most often conversion seems to occur from trichoepithelioma to BCC (12). This may constitute a diagnostic problem because BCC is the most common cancer form in the Caucasian population and is therefore also likely to occur at random in rare syndromic patients without a causal link being necessary. Therefore, lifelong UV exposure is an important confounder in BSS patients. In addition, benign adnexal tumors, especially trichoepitheliomas, can histologically mimic BCC (13). Therefore, misdiagnosis of adnexal tumors may lead to an overestimation of malignant degeneration. Our data show that those that developed malignant transformation were older. This may reflect either the general increased risk of malignancy with age or the slow-growing nature of the tumors. Correspondingly, the subjects in the group without malignancy were younger. Whether these patients have a long-term increased risk of developing malignancy is not known.

Data revealed overrepresentation of women in patients with BSS. Studies have shown that women are more likely than men to seek medical care and thus may have a lower detection threshold for malignancy (14). However, an underlying increased genetic

risk for women cannot be excluded.

In addition to tumors of skin appendages, BSS has also been infrequently associated with extracutaneous neoplasms; namely, basal cell adenomas and adenocarcinomas of the salivary and parotid glands and the breast (1, 5, 8, 9, 12, 15). Furthermore, a recent study reported an ovarian Brenner tumor positive for a *CYLD* mutation in a BSS patient (16). In 106 cases with BSS/MFT, two patients developed a salivary gland tumor in addition to skin tumors. Salivary gland involvement has so far been exclusively reported in patients with BSS. In most cases the parotid glands were involved, whereas submandibular glands were rarely affected. Furthermore, minor salivary glands and intranasal minor salivary glands were also described as infrequently affected. Multifocal presentation with simultaneous involvement of major and minor salivary glands is exceptional, but multifocal unilateral involvement of the parotid gland as well as bilateral metachronous and synchronous parotid lesions have been documented (11).

The literature provides little help in identifying the risk factors for the development of malignancy in BSS. Further and larger studies must therefore provide more comprehensive genetic data and detailed clinical data on patients with BSS, and it is suggested that a core set of variables always be reported.

The comprehensive review and clear clinical aim of the review are strengths. However, the body of literature available and its quality are limitations. The case reports did not contain all important clinical data such as ethnicity, comorbidity, and risk factors such as carcinogens (tobacco) (17), skin type, and lifetime sun exposure—all general factors that predispose to developing malignant skin tumors. It is strongly recommended that a more standardized template for reporting BSS be developed or an appropriately sized cohort be assembled for a prospective study.

Conclusions

This review summarizes the clinical, pathological, and genetic aspects of BSS. Although the vast majority of BSS cases do not develop malignancy, the recognition of this syndrome and its hereditary nature is of great importance to patients and their families. Our analysis revealed only age as a predictor of malignancy; however, this is also a general risk factor for development of malignancy and therefore of limited value as a screening tool.

Conflicts of interests

GBE Jemec has received honoraria from AbbVie, Chemocentryx, Coloplast, Incyte, Inflarx, Novartis, Pierre Fabre, and UCB for participation on advisory boards, grants from Abbvie, Astra-Zeneca, Inflarx, Janssen-Cilag, Leo Pharma, Novartis, Regeneron, and Sanofi for participation as an investigator, and speaker honoraria from AbbVie and Novartis. He has also received unrestricted departmental grants from Abbvie, Leo Pharma, and Novartis.

DML Saunte has received consultant fees for advisory board meetings by Leo Pharma, AbbVie, Jannsen Pharma, and Sanofi, and as a speaker for Bayer, Galderma, Astellas, Abbvie, and Leo Pharma.

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