

ORIGINAL CONTRIBUTION

Craniofacial Dermoid Cysts: Histological Analysis and Inter-site Comparison

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Introduction: Dermoid cysts are common, benign, embryologically derived soft tissue cysts that can arise at a variety of craniofacial sites. It is not known whether specific histological variations exist between the different craniofacial sites. This study aims to establish whether inter-site histologic differences exist between periorbital, nasal, scalp, and postauricular dermoid cysts and analyze these in context of their distinct embryological origin and varied clinical presentation.

Methods: A retrospective review of craniofacial dermoid cysts was performed. Using light microscopy with hematoxylin and eosin staining, histological appearance was directly compared between craniofacial sites.

Results: All (n = 16) cysts contained keratinizing, stratified squamous epithelial lining, intraluminal keratin, and hair. Sebaceous glands were commonly present (n = 13). Eccrine (sweat) glands were less common (n = 3). Structures of mesodermal origin were seen in three periorbital cysts. Only the six ruptured cysts showed evidence of inflammation.

Conclusions: Histological properties of dermoid cysts are conserved between craniofacial sites (periorbital, nasal, scalp, and postauricular). This reflects the consistency of ectodermal inclusion during early embryological development, which is independent of specific craniofacial site or surrounding anatomical structures.

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INTRODUCTION

Dermoid cysts are common congenital masses. They represent benign, embryologically derived soft tissue cysts. Craniofacial dermoid cysts comprise approximately 7 percent of all dermoids [1] and 60 percent of all facial cysts [2]. They typically present in infants as non-tender, subcutaneous masses along embryonal skin fusion lines. Common sites include periorbital (zygomaticofrontal suture), nasal (frontonasal suture and rhinion), intraoral (floor of mouth), scalp (anterior fontanelle and cranial sutures), and postauricular.

Histologic interrogation typically shows a keratinized stratified squamous epithelial lining. They are associated with mature adnexal structures, such as hair follicles and shafts, sebaceous glands, and eccrine (sweat) glands [3-5]. This differentiates them from epidermoid cysts, which are devoid of such adnexa. The glands and tissues are functional, resulting in the collection of intraluminal keratin. They may also be associated with underlying skull defects, perhaps predisposing to intracranial extension [5-8].

Craniofacial dermoid cysts develop at sites of aberrant ectodermal inclusion within the underlying mesoderm, during early embryological development. Closure of the neural tube occurs during weeks 3 to 4 of gestation [9], in a cranio-caudal sequence through complex patterns of embryonic folding along the midline symmetry axis [5]. Ventral folding and fusion of the five pharyngeal arches and the facial (frontal, maxillary, mandibular) processes then occur between weeks 4 and 8 of gestation. Abnormal folding of the ectodermal layer can occur along these embryonal lines of fusion [8]. Subsequent epithelial interactions between the superficial ectodermal and neural crest-derived mesodermal cells result in dermoid cyst formation with adnexal structures [5].

The varied topography of dermoid cysts is dependent on the precise timing and location of abnormal ectodermal inclusion dur-

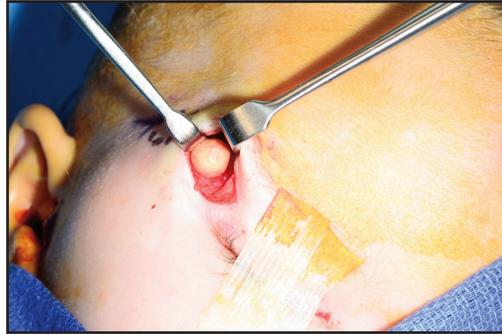


Figure 1. Intra-operative view during excision of an un-ruptured right periorbital dermoid cyst.

ing embryonic development [2,6]. Intraoral and postauricular dermoid cysts arise from abnormal ectodermal inclusion during fusion of the first and second pharyngeal arches [8]. Whereas nasal dermoid cysts arise from the midline nasal prominence [3,6], scalp dermoid cysts arise from the frontonasal prominence and periorbital dermoid cysts primarily from the zygomaticofrontal suture (external angle of the supraorbital ridge) [1,10].

It remains to be seen whether variations in the degree of ectodermal inclusion result in differences in the histology and structure of dermoid cysts at the various craniofacial sites. Such histologic differences may directly influence the severity of clinical presentation, including the potential for rupture or intracranial extension. It is also not known whether the specific site at which a dermoid cyst originates may influence its development and subsequent histological structure. Establishing this knowledge will help improve our understanding of the complex pathogenesis, with potential implications for optimizing diagnosis and management (timing and extent of surgical resection) of craniofacial dermoid cysts.

The purpose of this study is to analyze a series of craniofacial dermoid cysts from a variety of sites, with emphasis on histologic properties. Our main aim is to establish whether inter-site histologic differences exist between the various craniofacial dermoid cysts. Furthermore, we aim to characterize the significant histologic similarities and differences in context of their distinct embryological origin and varied clinical

Table 1. Patient demographics and craniofacial site.

Patient	Age (months)	Sex	Craniofacial site
1	31	M	Left periorbital
2	10	F	Right periorbital
3	14	M	Left periorbital
4	8	F	Right periorbital
5	21	F	Left periorbital
6	10	F	Right periorbital
7	17	M	Nasal glabella
8	36	M	Left nasal radix
9	34	F	Nasal glabella
10	13	F	Nasal glabella
11	10	F	Scalp
12	23	F	Scalp
13	10	F	Scalp
14	19	M	Scalp
15	16	M	Scalp
16	9	F	Right post-auricular

presentation. We hypothesize that the pathognomonic microscopic characteristics are preserved between sites and will review the common histologic features.

METHODS

A retrospective pathological review of craniofacial dermoid cyst excisions was performed. All dermoid cysts analyzed were excised surgically at Yale-New Haven Hospital, Plastic Surgery department, between 2011 and 2013 (Figure 1). In concordance with the Yale Human Investigations Committee, the study was deemed exempt from IRB review under federal regulation 45 CFR 46.101(b)(4). HIC Protocol #: 1306012149.

Patients' age at the time of surgical excision ranged from 9 to 36 months (Table 1). There were no intra- or postoperative complications noted, and there have been no episodes of recurrence to date.

Each specimen was sent for histological analysis in the Yale Surgical Pathology department. As per protocol, each specimen was fixed in formalin and embedded in paraffin. They then underwent routine hematoxylin and eosin staining. The slides were analyzed by light microscopy, using an Olympus BX40 microscope. Photomicrographs were taken of each specimen, using SPOT Basic software. This allowed us to analyze each specimen on a live camera feed to

Table 2. Distribution of cysts between craniofacial sites.

	n	%
Periorbital	6	38
Nasal	4	25
Scalp	5	31
Post-auricular	1	6

the computer screen and capture high-resolution photomicrographs, which were then processed into TIFF format. The histological structure was analyzed in detail and directly compared between cysts, with focus on the cyst lining, contents of the lumen, and associated adnexal structures.

RESULTS

Sixteen cases of dermoid cyst were analyzed histologically. The relative distribution of dermoid cysts between the craniofacial sites is 38 percent periorbital, 31 percent scalp, 25 percent nasal, and 6 percent postauricular (Table 2). This follows the relative distributions reported in previous studies [1,11-12].

Keratinized squamous epithelial lining (Figures 2 and 3a) was present in all (n = 16) cases (Table 3). This was consistent between all craniofacial sites, with varying degrees of epithelial differentiation between some cysts (Figures 3a and 3b). Furthermore, in-

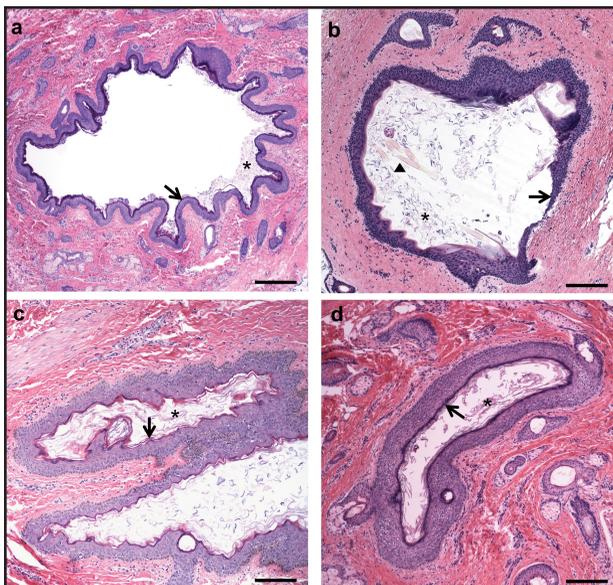


Figure 2. Low magnification photomicrographs demonstrating whole sections of individual dermoid cysts, from the different craniofacial sites analyzed. (Hematoxylin and eosin stain.) (a) Periorbital cyst (Magnification x20. Scale bar = 1mm). (b) Nasal cyst, (Magnification x40. Scale bar = 500 μ m). (c) Scalp cyst (Magnification x40. Scale bar = 500 μ m). (d) Postauricular cyst. (Magnification x40. Scale bar = 500 μ m). Despite variations in the physical size and shape of each cyst shown, these figures demonstrate the consistency of histological structures between sites. All cysts contain keratinizing stratified squamous epithelium (arrow) and intraluminal keratin (asterisk). Figure 3b also demonstrates intraluminal hair shafts (triangle), which are also seen in other specimens under high magnification. The associated adnexal structures are shown in higher magnification in Figure 3.

intraluminal keratin fragments (Figures 2 and 3a) were seen in all ($n = 16$) cysts.

Adnexal structures were also present in all ($n = 16$) cysts (Figures 3a and 3b). These include intraluminal hair shafts ($n = 11$) and intramural hair ($n = 13$). There was no observable instance of hair granulomata replacing portions of the cyst lining, as previously reported by Brownstein et al. [11]. Sebaceous glands were present in 13 cases. The glands were commonly ($n = 12$) part of a pilosebaceous unit; central hair follicles surrounded by a cluster of sebaceous glands (Figure 3b). In other specimens ($n = 3$), the sebaceous glands communicated directly with the cyst lumen (Figure 3c). Unlike the findings of Brownstein et al. [13], this was less common than the appearance

of well-formed pilosebaceous units (Figure 3b). These were mature and functional sebaceous glands, capable of producing thick sebaceous material to be secreted into the lumen.

The presence of eccrine glands was rare ($n = 3$). These were only seen in periorbital cysts. Furthermore, structures of mesodermal origin were seen in three periorbital cysts. These included smooth muscle fibers ($n = 3$), nerve fibers ($n = 1$), and adipose cells ($n = 1$). Striated muscle was frequently present in the surrounding tissue, but was never related to the cyst. Other structures foreign to the skin and subcutaneous tissue, such as thyroid, were also not seen.

Six cysts had ruptured. These all exhibited histological evidence of inflammation. There was significant infiltration of macrophages and lymphocytes, most concentrated around exposed hair follicles (Figure 3d). There were no signs of inflammation in any cyst that had not ruptured. Fur-

thermore, there was no difference in rupture rates between sites. An equal number of periorbital ($n = 2$), nasal ($n = 2$), and scalp ($n = 2$) cysts had ruptured.

One cyst showed evidence of intracranial extension. This was a midline, nasal glabellar dermoid cyst, which had extended clinically through a widened nasal septum into the crista galli. This cyst had very similar histological appearance to all others that did not extend intracranially.

DISCUSSION

Dermoid cysts are benign soft tissue cysts of embryonic origin that arise along lines of skin fusion. They form as a result of abnormal ectodermal sequestration during early embry-

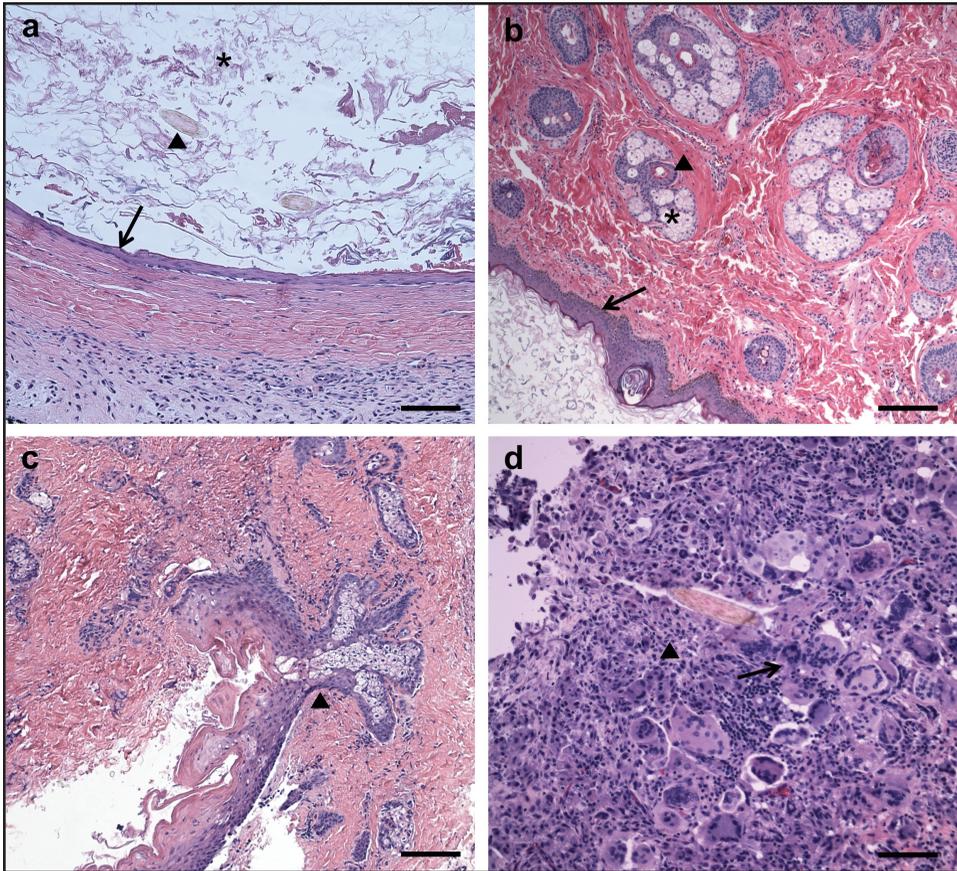


Figure 3. High magnification photomicrographs demonstrating histologic structures within the dermoid cysts (hematoxylin and eosin stain). (a) Photomicrograph of well-differentiated keratinizing stratified squamous epithelial lining (arrow) complete with an organized spinous and granular layer. The intraluminal keratin (asterisk) and hair shafts (triangle) are also demonstrated. (Magnification x200. Scale bar = 100 μ m.) (b) Intramural adnexal structures include numerous pilosebaceous units, containing sebaceous glands (asterisk) with an associated hair follicle (triangle). The epithelium (arrow) appears to be less well differentiated than (a), with parakeratosis. (Magnification x100. Scale bar = 200 μ m.) (c) Sebaceous glands may occasionally communicate directly with the cyst lumen (triangle). (Magnification x100. Scale bar = 200 μ m.) (d) Ruptured cyst with inflammatory reaction. Infiltration of macrophages (arrow) and lymphocytes (triangle) is associated with an exposed hair shaft. This can be compared with un-ruptured cysts (a), (b), and (c), which do not demonstrate an inflammatory reaction. (Magnification x200. Scale bar = 100 μ m.)

ological development [8,14-15]. With regard to craniofacial development, ventral folding and fusion of the five pharyngeal arches and facial processes occurs between weeks 4 and 8 of gestation, following closure of the neural tube [9]. The varied topography of craniofacial dermoid cysts can be correlated to the initial position of ectodermal inclusion within the underlying mesoderm [5].

In the current study, each of the common craniofacial sites (previously de-

scribed), except intraoral, were analyzed and compared. Despite the small sample size (n = 16), the dermoid cysts studied are well distributed between craniofacial sites (Table 2). Furthermore, to the authors' knowledge, there is no other study in the literature directly comparing histology of dermoid cysts between craniofacial sites. This is an important concept to understand in context of the distinct embryological developments between sites and varied clinical presentation

Table 3. Histological findings in relation to craniofacial site.

Case	Craniofacial site	Squamous epithelium	Intraluminal keratin	Intraluminal hair	Intramural hair	Sebaceous glands	Eccrine glands	Cartilage	Muscle	Nerve	Fat	Rupture	Inflammation
1	Periorbital	Y	Y	Y	Y	Y			Y				
2	Periorbital	Y	Y	Y	Y	Y							
3	Periorbital	Y	Y	Y	Y	Y	Y		Y	Y		Y	Y
4	Periorbital	Y	Y	Y	Y	Y			Y		Y		
5	Periorbital	Y	Y	Y	Y	Y	Y					Y	Y
6	Periorbital	Y	Y	Y	Y	Y	Y					Y	Y
7	Nasal glabella	Y	Y	Y		Y						Y	Y
8	Nasal radix	Y	Y	Y								Y	Y
9	Nasal glabella	Y	Y	Y	Y	Y							
10	Nasal glabella	Y	Y	Y	Y	Y							
11	Scalp	Y	Y	Y	Y	Y							
12	Scalp	Y	Y	Y	Y	Y							
13	Scalp	Y	Y	Y								Y	Y
14	Scalp	Y	Y	Y	Y	Y						Y	Y
15	Scalp	Y	Y	Y	Y								
16	Post-auricular	Y	Y	Y	Y	Y		Y				Y	

Table 4. Comparison of histologic findings with Shields et al. [13]

	Reissis et al., 2014 Craniofacial dermoid cysts	Shields et al., 1997 Orbital dermoid cysts
Squamous epithelium*	100%	84%
Hair shafts**	100%	99%
Sebaceous glands	81%	75%
Sweat glands	19%	20%
Inflammation	38%	38%

*Keratinizing stratified squamous epithelium

**Intraluminal or intramural

during early childhood. It is previously unknown whether the specific site at which a dermoid cyst originates may influence its development and subsequent histological structure.

Our results demonstrate that the histopathological appearance of dermoid cysts is largely consistent between the periorbital, nasal, scalp, and postauricular sites. This suggests that craniofacial site does not directly affect histological structure of individual dermoid cysts. Given the universality of hair and intraluminal keratin as part of the dermoid cyst (Table 3), there is particularly no variation between craniofacial sites in these respects.

Shields et al. [14] described pathologic correlations within a sample of orbital dermoid cysts. Table 4 compares the relative distributions of histological structures between the results of Shields et al. and those of the current study. The histological appearances remain highly comparable between samples, despite the varied craniofacial sites studied in the current study. This further suggests that histology is preserved between sites.

The histological consistency between craniofacial sites is interesting from an embryological standpoint. Dermoid cysts all have similar embryological origins [12,16-17]. Abnormal sequestration and inclusion of the surface ectoderm occurs, with failure to separate from underlying mesoderm. This occurs along lines of embryonal skin fusion, following patterns of folding [18]. However, by definition, this pattern of development varies slightly at different craniofacial sites [5]. For example, periorbital dermoids most commonly occur as a result of ectodermal

sequestration at lines of fusion along the zygomaticofrontal suture [8,10], whereas nasal cysts develop within the prenasal space (between the cartilaginous wall of the nose and nasal bones) [6,17], originating from the nasal placode. Furthermore, the timing of embryological events also varies between different craniofacial sites. Periorbital cysts develop early, between 3 and 5 weeks of gestation [19], whereas nasal cysts develop toward the end of the second month (week 8) of gestation [7] during intramembranous ossification of the nasal capsule [17]. Dermoids of the scalp are also thought to arise during intramembranous ossification of the cranial bones [19]. Thus it is interesting that histology is conserved between craniofacial sites despite these underlying variations in the specific structures involved and the timing of embryological development.

Keratinizing squamous epithelium is of ectodermal origin, whereas dermal and adnexal structures are derived from mesodermal neural crest cells [5]. Therefore, for these structures to co-exist within a dermoid cyst, the initial episode of ectodermal inclusion and subsequent ectodermal-mesodermal cellular interactions must occur early during embryological development, before the commitment of the different tissues [18]. This correlates with the completion of the embryonic period at week 8 of gestation, before transition into the fetal period. Thus, as long as the ectodermal inclusion event occurs before week 8, it appears that dermoid cysts will develop similar histologic structure irrespective of the specific craniofacial site.

Naturally, there were some subtle histologic differences noticeable between the

craniofacial sites. Three of the six periorbital cysts analyzed contained either smooth muscle fibers, adipose cells or nerve fibers. These were not apparent in cysts from any other site. The relatively early development of periorbital cysts may account in part for the increased appearance of mesodermal structures within them. Earlier sequestration of ectoderm within the mesoderm may allow these two germ layers to become relatively contiguous with one another, thus increasing the prevalence of both ectodermal and mesodermal structures within the periorbital cyst.

Furthermore, there were differences in the degree of differentiation seen in the epithelium of some cysts. Periorbital cysts had a predominance of well-differentiated epithelium (Figure 3a), complete with organized spinous and granular layers. However, cysts from other locations, such as nasal (Figure 3b), often had less well-differentiated epithelium with a degree of parakeratosis. This also correlates with the timing of embryological development. As periorbital dermoid cysts tend to develop earlier, they may undergo further maturation and differentiation of individual structures contained within the cyst. As embryological development progresses, the cyst wall matures and is more likely to differentiate into the characteristic layers of normal epidermis. Therefore, the subtle difference in timing between the development of periorbital cysts and those from other craniofacial sites may also account for their increased expression of differentiated epithelium.

The tissues produced within dermoid cysts are equivalent to those of normal mature epidermal tissue. However, they arise in an aberrant location, enclosed within the cyst epithelial lining. They remain indolent in this fashion and may increase in size slowly due to production of keratin and sebaceous material [1]. Rupture may occur spontaneously, secondary to local trauma or at the time of surgical excision. This causes acute exposure of the mature epithelial and mesodermal structures to the surrounding tissues, with pronounced local inflammation. Giant cells (monocytes and

macrophages) and lymphocytes are sequestered to the site, with greatest concentrations around the exposed hair follicles (Figure 3d). This can be compared histologically with un-ruptured cysts (Figures 2 and 3a,b,c), which do not show any inflammatory response to the structures within the cyst, including intraluminal or intramural hair. Since no signs of inflammation were seen in intact cysts, it is suggested that inflammation occurs as a result of rupture, rather than as a cause of rupture.

Furthermore, there was no correlation between the presence of intramural or intraluminal hair and inflammation. Three of the ruptured cysts contained intraluminal hairs only, two contained intramural hairs only, and one contained both (Table 3). Therefore the precise location of hair shafts does not seem to relate to the propensity for cyst rupture and subsequent inflammation. Inflammation does not occur in response to hair shafts that are contained within an intact dermoid cyst. However, inflammation does occur following cyst rupture. This is most likely due to the acute exposure of cyst contents, such as the hair shafts and keratin, to the surrounding cells. These differentiated tissues, which were previously isolated within an intact cyst wall, would appear foreign to the native local tissues following cyst rupture and cause the subsequent local inflammatory reaction.

Chronic inflammation has previously been described within dermoid cysts [14,20]. This can potentially cause damage to the underlying tissues and structures. However, these effects were not seen in the current study. This is in contrast to the findings of Abou-Rayyah et al. [21], who report histological evidence of inflammation in more than two-thirds of unruptured periorbital cysts. This was accounted for by leakage of intraluminal keratin into the surrounding tissues. However, this phenomenon was not observed in the current study. It is noted that the relatively young age group of patients in the current study may have been a factor in this difference [14]. Still, this result supports the idea of dermoid cysts as benign and structurally isolated

from surrounding tissues, without inflammatory reaction, unless ruptured.

Intracranial extension of dermoids does rarely occur. This is more common with midline nasal and scalp cysts [5-8]. The one nasal glabellar cyst that extended intracranially in the current study had the same basic histological structure as all other cysts. There are no demonstrable histological differences between cysts that extend intracranially and those that do not. This suggests that intracranial extension is caused by failure of cranial sutures to fuse completely and the resulting skull defects [5-8], rather than structural or functional properties of the cysts themselves.

CONCLUSION

Craniofacial dermoid cysts are common benign soft tissue cysts of embryonic origin. Their histologic properties are conserved between craniofacial sites (periorbital, nasal, scalp, and postauricular). This suggests that the craniofacial site does not directly affect histologic structure of individual dermoid cysts. Stratified keratinizing squamous epithelium with hair is present in all cysts. Adenexal derivatives may be present across sites, whereas periorbital cysts exhibit a greater preponderance of mesodermal structures. These findings reflect the consistency of ectodermal inclusion as the pathogenesis of dermoid cysts. This occurs early during embryological development (up to week 8) and is independent of specific craniofacial site or surrounding anatomical structures.

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