Chondrosarcoma of the Femur with Histology-Imaging Correlation of Tumor Growth
Preliminary Observations Concerning Periosteal New Bone Formation and Soft Tissue Extension

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Abstract

The objective of this study was, in chondrosarcoma (CHS) of the femur, to evaluate by radiologic-pathologic correlation, the degree of tumor growth, cortical destruction, periosteal reaction, and soft tissue extension present.

Materials and Methods: Eight cases of histologically proven CHS of the femur were studied. All cases were resected, evaluated histologically with coronal slabs, and compared with radiographs and magnetic resonance imaging (MRI) scans. In two resected specimens, the tumors were studied in more detail; along with coronal slabs, axial sections of the remaining anterior and posterior halves of both tumors were taken, and the bone specimens were X-rayed and examined histologically.

Results: CHS initially involved the medullary cavity and subsequently destroyed the cortex; first, by endosteal scalloping and, second, by subsequent invasion and destruction of the cortex. During this process, there was periosteal new bone formation (PNBF), with increased cortical thickness, the degree of which often correlated with the degree of cortical destruction. In the areas of cortical thickening of three cases, a “grey line” was seen on MRI that separated the cortex from the periosteal new bone; the line, in reality, is a space between the two structures. The presence of this line suggests that the tumor does not extend beyond the cortex. PNBF occurred in all cases and varied in thickness. It frequently developed independent of direct periosteal tumor involvement. The periosteum of one case contained porotic bone with interposed marrow fat, which was easily misinterpreted as tumor extension on MRI. Expansion and remodeling of the femoral diaphysis in CHS, with widening of the medullary cavity, is usually due to extensive cortical destruction with PNBF. Soft tissue extension was present in five cases and apparently occurred by two different mechanisms: direct tumor destruction of the cortex and periosteum, with extension into the soft tissues; and subtle MRI occult tumor permeation through the periosteum. As far as we know, a first literature histologic description of the thickened CHS periosteum also was accomplished.

Conclusion: PNBF is a common imaging manifestation of CHS of the femur, which correlated with the degree of cortical destruction. A grey line between the cortex and periosteum is an MRI finding described in this study and may facilitate the evaluation of periosteal thickening and tumor invasion in CHS. PNBF often occurs in the absence of direct periosteal involvement. Periosteal imaging abnormalities suggestive of tumor infiltration should be interpreted with caution on MRI, and early soft tissue extension in CHS may be difficult to determine on MRI.

Chondrosarcoma (CHS) is the second most frequent primary malignant tumor of bone after osteosarcoma. Conventional intramedullary CHS is the most common type of CHS and very frequently involves the femur, which represents from 20% to 35% of cases. Radiologic abnormalities that favor CHS of long bones are mineralized chondroid matrix, deep endosteal scalloping, cortical destruction and thickening, periosteal new bone formation (PNBF), and soft tissue extension. It is known
in low-grade CHS that cortical thickening is due to the deposition of PNBF on the outer cortex as a consequence of cortical destruction and microscopic permeation by tumor. While there is some information in the literature about the mechanism of PNBF, there is a paucity about the distinction between PNBF and cortical bone and about PNBF’s relationship to soft tissue extension. We have observed histologically that PNBF can occur in CHS in the absence of direct tumor infiltration of the periosteum.

The purpose of this preliminary radiologic-pathologic study was three-fold: first, to investigate in CHS of the femur the extent of cortical destruction and PNBF and the role played by the tumor in the development of PNBF; second, to evaluate by magnetic resonance imaging (MRI)-histologic correlation the boundary between cortical and periosteal bone; and third, to describe the process of soft tissue extension in CHS, in correlation with MRI.

Materials and Methods

Eight resected specimens of CHS of the femur were selected from the files of NYU Hospital for Joint Diseases. Only tumors of the femur were chosen for the study, because this bone has a prominent cortex and allows a better evaluation of cortical-tumor interaction. All patients had preoperative radiographs and MRI. Table 1 contains the clinical, radiologic, and pathologic data of all eight cases. The eight resected specimens were studied histologically, including a coronal bone slab with specimen radiograph for each case. Bone sections were obtained from the slabs and were mapped in the corresponding specimen radiographs. The histological sections were correlated with the corresponding preoperative radiographs, specimen radiographs, and MRI scans. Two of the resected specimens (Cases 1 and 2) were examined in more detail. Besides the coronal slabs, axial sections of the remaining anterior and posterior halves of each femur were obtained, the individual bone sections were X-rayed, labeled accordingly, and processed histologically. The histologic data allowed for the periosteum (thickness and tumor involvement) to be described using a semi-quantitative scale from 1 to 4 (the highest) (Table 1). Soft tissue extension of the tumor was calculated by linear measurement of the largest extracortical extension from gross or histological examination.

In all eight resected cases, a distinction between cortical and periosteal bone was attempted histologically by light microscopy and polarized light microscopy. The histologic sections were correlated with the corresponding specimen radiographs and MRI.

Results

Histology of Periosteal New Bone Reaction (PNBF)

Under histologic examination of PNBF free of tumor, a blue cement line was frequently seen on Hematoxylin and eosin (H&E) stains, separating the cortex from the periosteum in the femoral diaphysis, on both axial and coronal sections of the bone. In the sections examined, periosteal bone tended to be less organized than cortical bone, with irregular architecture. Under polarized light microscopy and especially axial sections, the Haversian systems of the periosteum were of different sizes, had variable degrees of maturation, and contained immature bone. Some spaces lack circumferential lamellae. In addition, thick layers of bone could be seen containing lamellae, which were arranged parallel to the bone surface. Small bone spaces usually contained capillary vessels. In some cases, the periosteum had large spaces composed of trabecular bone with capillary vessels, fat, and hemopoietic marrow. There were also dilated and blood-filled capillary vessels. As we describe later on, large and elongated bone spaces were also present in some cases at the cortical-periosteal junction. It should be mentioned that at times it was extremely difficult or even impossible to distinguish cortical from periosteal bone at the cortical-periosteal junction.

Pathologic and Radiologic Resected Specimens

Cases 1 and 2 are described in detail. The clinical-pathologic-radiologic data of the remaining cases are included in Table 1. All CHS tumors were grade 1 or 2. No grade 3 tumors were evaluated.

Case 1

Coronal sections of the femur revealed a lobulated cartilaginous tumor with extensive calcification. The tumor occupied the diaphysis, metaphysis, and part of the epiphysis, and extended to the articular end of the bone, measuring 24 cm in length and 4.5 cm at its widest aspect. In the proximal part of the lesion, the medullary cavity was filled with tumor and the CHS abutted on the endosteal surface, which histologically was essentially normal and without periosteal response. This area measured 1.5 cm in length.

Cortical involvement by tumor was manifested histologically by endosteal erosion and progressive cortical destruction by tumor, which abutted onto eroded bone and also permeated into haversian and Volkmann’s canals. (Figs. 1 and 2A) The degree of cortical destruction of the diaphysis was not uniform.

PNBF was a response to cortical destruction from infiltration of the cortex by the CHS. Except for the proximal 1.5 cm of the tumor, PNBF was seen throughout the length of the femoral diaphysis. The degree of PNBF was variable; however, there was some correlation with the degree of cortical destruction.

At or near the junction between the cortical and periosteal bone, large flattened bone spaces were seen histologically (Fig. 2A). These spaces were devoid of tumor and were recognized in the specimen radiographs as dark lines at the cortical-periosteal junction (Fig. 2B). The same differentiation between the cortex and periosteal...
Table 1  Clinical-Radiologic-Pathologic Data of Conventional Chondrosarcoma of the Femur

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (Years)/Gender</th>
<th>Site/Size</th>
<th>Histology Grade</th>
<th>Radiographs</th>
<th>MRI</th>
<th>Periosteum (Diaphysis)</th>
<th>Tumor Involvement</th>
<th>Soft Tissue Extension</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70/M</td>
<td>Lft diaphysis and distal femur, 24 cm</td>
<td>1</td>
<td>++</td>
<td>+</td>
<td>Violated</td>
<td>+</td>
<td>+</td>
<td>2 cm. distal diaphysis Single histologic area suggestive of pre-existing enchondroma</td>
</tr>
<tr>
<td>2</td>
<td>60/M</td>
<td>Lft diaphysis and distal femur, 20 cm</td>
<td>1</td>
<td>+++</td>
<td>+</td>
<td>+/−</td>
<td>−</td>
<td>4 (1.2 cm)</td>
<td>0.2 cm. distal diaphysis</td>
</tr>
<tr>
<td>3</td>
<td>76/M</td>
<td>Rt proximal metaphysis and diaphysis, 13 cm</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td>Violated</td>
<td>+</td>
<td>3 (0.8 cm)</td>
<td>4 cm. proximal diaphysis</td>
</tr>
<tr>
<td>4</td>
<td>58/M</td>
<td>Rt proximal diaphysis, 13 cm.</td>
<td>1</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>2 (0.4 cm)</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>56/M</td>
<td>Lft proximal metaphysis and diaphysis, 11 cm</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>2 (0.5 cm)</td>
<td>7 cm. Proximal metaphysis</td>
</tr>
<tr>
<td>6</td>
<td>74/M</td>
<td>Rt proximal metaphysis and diaphysis, 25 cm</td>
<td>2</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>−</td>
<td>2 (0.3 cm)</td>
<td>1 Minimal focal tumor 11 cm. proximal metaphysis</td>
</tr>
<tr>
<td>7</td>
<td>67/F</td>
<td>Rt proximal metaphysis, and diaphysis, 12 cm</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>Intact but thinned +</td>
<td>−</td>
<td>2 (0.3 cm)</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>72/F</td>
<td>Lft Proximal epiphysis, metaphysis and diaphysis, 11 cm</td>
<td>2</td>
<td>++</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>1 (0.2 cm)</td>
<td>No</td>
</tr>
</tbody>
</table>

Radiology: abnormal, +; normal, −; Histology: periosteal thickness and periosteal tumor involvement. Semi-quantitative scale of 1 to 4 (highest)
bone could also be demonstrated on MRI by a delicate line within the bone running parallel to the surface. This line, which we have termed the “grey line,” due to its imaging appearance, had an intermediate intensity signal on both T1-weighted and T2-weighted images and was observed in both axial and coronal images (Figs. 2C and

Figure 1 Case 1. A, AP radiograph of the distal left femur, showing a lytic lesion, with ill-defined margins, intramedullary calcifications, proximal cortical thickening, and deep scalloping (arrowhead). B, Photograph of the specimen, showing extensive tumor that involves most of the shaft and the distal femur. Note the presence of cortical thickening in the midshaft, different degrees of endosteal scalloping, and a deep scalloped area (arrowhead), with focal widening of the medullary cavity (see also Fig. 1A). C, Micrograph of CHS, grade I, showing marrow permeation, with entrapment of pre-existing bone (arrow) (H&E, 70X).

Figure 2 Case 1. A, Histologic slide of an axial anterior section of the mid cortex, showing endosteal erosion by tumor (T), associated with periosteal response along the outer cortex. Large bone spaces separate the periosteum from the cortex (arrows). The spaces contain fat, capillaries, and loose fibrous tissue that includes rare lymphocytes. The infiltrating edges of the tumor do not reach the periosteal surface (H&E, 3X). B, Specimen radiograph of bone section (3 mm thick), comparable to Fig. 2A, with cortex and periosteal bone (right aspect) separated by a dark line (arrowheads). C, Axial FSE T2-weighted image (TR 4200/TE 85) from region demonstrated in Figs. 2A and B, showing the CHS as a high intensity signal interrupted by spotty low intensity foci, representing tumor calcifications. A “grey line” is seen only in the lateral circumference of the cortex (arrow), which separates the cortex from the periosteal new bone (see also Figs. 2A and B).
It should be emphasized that this grey line, seen on MRI, was not present in all areas of cortical thickening; it was absent when the periosteum was firmly attached to the cortex, as we noted histologically and also in the specimen radiograph in the present case.

Focal expansion of the distal shaft was seen laterally, with some widening of the medullary cavity (Figs. 1A, B). This was due to destruction of the cortex and replacement with periosteal bone (Fig. 3).

Tumor infiltration of the periosteum was seen histologically in several areas, particularly in the anterodistal region of the diaphysis. In other areas, the CHS did not extend to or invade the periosteal bone, particularly the proximal region.

Soft tissue extension of CHS was present only in the anterodistal region of the diaphysis. In that area, there was destruction of the cortex and periosteum, and the tumor invaded into the soft tissue in an extension of 2 cm in length and 1 cm in width (Fig. 4).

Sections of the tumor at the metaphyseal-epiphyseal region demonstrated localized cortical permeation, with focal tumor infiltration into the soft tissues, as well as into the knee through the intercondylar notch. In the distal region of the CHS, a circumscribed area of calcified cartilage matrix was seen, containing lacunae with necrotic cells, which suggested a pre-existing enchondroma. This area was surrounded by viable CHS.

Case 2
Coronal and axial sections revealed a CHS, with involvement of the diaphysis and part of the left distal femur, measuring 20 cm in length, with extension to within 1 cm of the distal articular cartilage. The tumor was grayish white and cartilaginous, with areas of calcification, and there was, histologically, tumor permeation of the cortex. The femur had an irregular outer surface and was markedly enlarged; the widest area measured almost 6 cm. This was due to prominent periosteal thickening of the diaphysis, which started 4 cm proximal to the intramedullary location of the tumor and extended to the distal metaphyseal region. The periosteal bone measured up to 1.2 cm in thickness (Figs. 5A-C).

Periosteal invasion by CHS was limited to the middle and anterodistal part of the diaphysis and consisted of several tumor foci, varying from 0.1 x 0.1 to 1.8 x 0.6 cm. Tumor was also seen in the posterior periosteum, a single small area measuring 0.4 x 0.3 cm and located at the junction with the cortex. Some of these foci of peri-
osteal permeation produced minimal bone destruction. Only a few tumor areas in the periosteum were seen in the imaging studies (Figs. 5D,E). In addition, other abnormal periosteal areas were noted, containing porotic bone and fat (Figs. 5D,E and 6).

Soft tissue extension in Case 2 was very small and occurred by invasion of the periosteum by linear rows of tumor that permeated through Haversian canal-like channels (Fig. 7). A small focus of tumor measuring 0.2 x 0.2 cm was the only tumor noted outside the bone (Fig. 7B). This type of soft tissue invasion was subtle and was not identified in the specimen radiographs or on MRI.

Specimen radiographs taken from the coronal, anterior, and posterior axial sections of the femur show only a few linear disruptions at the cortical-periosteal region. Histologically, there was close attachment between the cortex and periosteum, which often made it difficult or impossible to distinguish between them (Figs. 6B and 7B). No spaces separating the cortex from the periosteum were seen. For data on Cases 3 to 8, see the clinical-radiologic-pathologic data provided in Table 1.

**Discussion**

PNBF is a common feature of CHS, together with matrix mineralization, deep endosteal scalloping, bone remodeling, and associated soft tissue mass.\(^3\) It occurs radiographically in 51% of cases.\(^1\) Lodwick\(^4\) was one of the first investigators to describe in detail, in 1971, PNBF in bone neoplasms. He noted radiographically that in slow growing tumors there is destruction of the endosteal cortex, with associated PNBF forming a consolidated thick layer of new bone.\(^4\) PNBF results in cortical thickness, which displays radiographically in 47% of CHS.\(^3\) These processes of cortical thickening with remodeling and PNBF, are responses of the affected bone to contain the CHS in the marrow cavity.\(^2\) Lodwick\(^4\) also indicated that “periosteal new bone serves to encapsulate the tumor and meet weightbearing stress, despite destruction of original cortex by tumor.” Other authors have noted the periosteum is likely more important in bone strength than has been recognized.\(^5\)

Based on our experience in this limited number of eight cases of CHS, grades 1 and 2, the following observations related to PNBF, soft tissue extension, and cortical remodeling in CHS of the femur were made.

**MRI Differentiation Between PNBF and Original Cortex**

The periosteum can often be differentiated from the cortex on MRI by a separate “grey line,” which was seen on MRI in Cases 1, 3, and 5. When this “line” is present, a distinct histologic pattern was often seen at the cortical-periosteal junction. To the best of our knowledge, the “grey line” has
not been reported prior in MRI of CHS of long bone. Presence and evaluation of this space, seen radiologically as a “grey line,” may facilitate an understanding of the actual degree of periosteal thickening, which is an important radiologic feature of CHS of the femur. The presence of this “line” also suggests that the tumor does not extend beyond the cortex, which should be confirmed by additional studies. The “grey line” was absent when the cortex was destroyed. More frequently, however, this “line” was absent or subtle probably because the periosteum was attached and consolidated to the cortex, as we found in five of the eight cases.

It should be mentioned that the “grey line” seen by MRI was present only in the diaphysis of the femur but was absent in the proximal and distal end of the femurs, probably because the original cortex in that area was attenuated, and the periosteal bone response was not significant. Therefore, when this sign is assessed, it may only be reliably used for the diaphysis regions.

**PNBF and Its Relationship to Tumor Permeation of the Femoral Cortex**

CHS of long bones invades from the medullary cavity to the cortex by endosteal erosion, which is the first step by the tumor to extend to a second compartment. This is fol-

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**Figure 5** Case 2. A, AP radiograph, showing CHS with intramedullary calcification and prominent periosteal reaction. No endosteal scalloping is definitively seen; however, note the intra-periosteal linear luencies giving a multi-laminated appearance. B, Lateral radiograph of the same case, also showing luencies within ossified periosteum (arrow). C, Gross photograph of tumor, showing a grayish white, partially lobulated CHS, with dark brownish areas involving part of the diaphysis and distal femur. There is dense PNBF. Note focal porotic area of periosteum (F), which corresponds to similar areas in Figs. 5D and E and represents fat. There is a fragment of cement from previous biopsy inside the medullary cavity. D, Specimen radiograph of the same case, demonstrating prominent periosteal bone and absence of endosteal scalloping. The lucent areas in the thick periosteum represent tumor (T), fat within porotic bone (F) or a combination of both (F and T). The tumor indicated at the right (T) involves mainly the medullary cavity. E, Coronal T1-weighted MRI of the femur, demonstrating a homogenous T1 signal, with expansion of the medullary cavity and cortical thickening. Note abnormal signal within periosteal new bone, representing fat (F) or tumor admixed with fat (F and T), the former higher in signal intensity.
lowed by microscopic permeation of the Haversian and Volkmann’s canals, with cortical destruction (57% of CHS on radiographs). Based on our observation of the eight resected tumors, we found that in all cases (CHS grades 1 and 2) the tumor abutted on the eroded bone, but we also noted in these cases the presence of varying amounts of fibrovascular tissue interposed between the tumor and bone. This is different from the observations made by Sanerkin, who found in low-grade CHS tumor abutment to the bone without intervening tissue or cells. Very rare osteoclasts were noted in our cases at the tumor-bone interface.

PNBF is a reactive process that results initially from microscopic tumor invasion of the cortex and, eventually, also from periosteal invasion. Hudson has previously documented at low magnification the early stages of endosteal scalloping and PNBF. All of our resected CHS specimens demonstrated evidence of PNBF, which varied from 0.2 to 1.2 cm in thickness. Tumor invasion from the cortex into the periosteum, as demonstrated histologically, occurred in seven out of eight cases and varied from minimal to moderate. However, in each of the seven cases, there were large areas of the periosteum that were free of tumor. In one case, the periosteum was not involved by tumor (Table 1).

PNBF results from stimulation of the mesenchymal stem cells of the cambium layer of the periosteum, which become osteoprogenitor cells and differentiate into osteoblasts. In a comprehensive review of the literature, Lakey and colleagues recently proposed that PNBF has a common his-
topathologic mechanism that involves vascular endothelial growth factor (VEGF), regardless of the patient’s age or different etiologic conditions, saying “These conditions trigger a plethora of factors which directly or indirectly stimulate VEGF in promoting angiogenesis, as well as periosteal and mesenchymal bone proliferation necessary for new bone formation.” According to these investigators, “VEGF is the most likely common mediator of the pathways that lead to PNBF.”

Our studies demonstrate that PNBF in CHS can occur independent of periosteal tumor involvement and is present during cortical destruction before the tumor reaches the periosteum. It is possible that PNBF in CHS develops, at least initially, following the same histopathologic mechanism proposed by Lakey and coworkers, through chemical mediators that may be produced or induced by the CHS.

**Presence of Porotic Bone and Fat in the Periosteum**

Another interesting finding in the thickened periosteum of one case (Case 2) was the presence of porotic bone containing fat. Although uncommon, this finding might be misinterpreted on MRI as tumor invasion. Therefore, MRI abnormalities suggestive of periosteal involvement by CHS should be interpreted with caution.

**Different Patterns of Cortical and Periosteal Destruction Associated with Soft Tissue Extension**

Soft tissue extension in conventional CHS occurs frequently, and MRI is the best modality to identify it in long bone CHS (76% of cases). Reports in the literature show that at the site of CHS with soft tissue extension, MRI demonstrates, in most cases, deep endosteal scalloping with cortical permeation, disruption, or penetration. Soft tissue extension was present in five of the resected specimens (Cases 1, 2, 3, 5, and 6) and occurred in the diaphysis and metaphysis. In Cases 1 and 2, the soft tissue extension was limited and allowed an initial detailed radiologic-histologic evaluation. Based on our limited experience, it appears that in the femoral diaphysis there are at least two different mechanisms of bone destruction with soft tissue extension: first, one in which the tumor destroys the cortex and periosteum, recognized on MRI by endosteal scalloping, cortical destruction, and soft tissue extension (Case 1); and, second, a type of soft tissue extension where the tumor permeates into the periosteum through haversian canal-like channels in a microscopic linear fashion, which it difficult to recognize on MRI, as in our Case 2.

The first mechanism of soft tissue extension is probably the most common. The other cases of soft tissue extension in our series (Cases 3, 5, and 6) had larger areas of cortical and periosteal destruction at clinical presentation, and therefore, the initial mechanisms of soft tissue extension could no longer be determined. It is interesting to know that Brien and associates, in a brief comment about advanced CHS of the femur, indicated that soft tissue extension developed through focal cortical destruction or by permeation through the haversian systems. Additional cases of CHS of long bones with early soft tissue extension should be studied in order to better understand this process. Based on our limited experience, we found in the diaphysis no relationship between the degree of periosteal thickening and the size of soft tissue extension.

Soft tissue extension of CHS involving the metaphyseal region, such as Cases 5 and 6, probably occurs earlier than in the diaphyseal region, because the cortex in the former is thinner than the diaphyseal cortex.

**CHS with Bone Expansion and Widening of the Medullary Bone**

CHS may show radiological expansion of the bone with widening of the medullary cavity, which is due to remodeling and destruction of the cortex with PNBF. A new shell of periosteal bone develops that separates the tumor from the soft tissue. This finding was demonstrated in the lateral cortex of Case 1, and was also observed by one of the authors (GCS) in other cases of CHS outside this study.

**Conclusion**

In this limited radiologic-pathologic study of CHS of femur, we describe on MRI a “grey line” representing a space between the cortex and periosteum. This finding may help others to evaluate the degree of periosteal thickening in CHS. The presence of this line also suggests that the tumor does not extend beyond the cortex. We believe that PNBF can develop in CHS independently from direct periosteal tumor involvement. This study appears to identify two different mechanisms of bone destruction with soft tissue extension in CHS: one with conspicuous areas of cortical and periosteal destruction, which can be recognized on MRI; and another mechanism of subtle microscopic tumor permeation through the periosteum, which makes it difficult to recognize on MRI. Additional studies are needed to further confirm and expand these findings. This study further accomplished a histologic description of the thickened periosteum in CHS, which, to our knowledge, is lacking in the literature.

**Disclosure Statement**

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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