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Clear cell papillary cystadenocarcinoma of the epididymis: a case report and immunohistochemistry of markers for renal cell carcinoma

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Summary. Neoplasms of the epididymis are uncommon, and malignant tumors are extremely rare. We report a case of clear cell papillary cystadenocarcinoma of the epididymis presenting with a long history of painless scrotal mass on the left side. Immunohistochemical markers for clear cell renal cell carcinoma (RCC) were examined to distinguish between clear cell papillary cystadenocarcinoma of the epididymis and metastatic clear cell renal cell carcinoma. The present case was positive for cytokeratin-7, PAX2, vinculin, vimentin and carbonic anhydrase IX. Expression of CD10 was focally observed. In contrast, no immunoreactivities for α-methylacyl-CoA racemase, RCC marker, glutathione S-transferase α or C-KIT were detected. The immunophenotypic profile of clear cell papillary cystadenocarcinoma of the epididymis closely resembles that of clear cell papillary RCC, although the immunohistochemical markers tested in this study are useful to make a differential diagnosis between clear cell papillary cystadenocarcinoma of the epididymis and metastatic clear cell RCC.

Key words: Cystadenocarcinoma, Epididymis, Molecular marker, Renal cell carcinoma

Introduction

Primary epididymal neoplasms are rare, accounting for approximately 5% of intrascrotal neoplasmas (Aydin et al., 2005; Richie and Steele, 2007; Odrzywolski and Mukhopadhyay, 2010). Epididymal tumors are usually benign; the majority of these tumors are adenomatoid tumor and leiomyoma, followed by clear cell papillary cytadenoma and a variety of benign soft-tissue tumors. Approximately one quarter of epididymal tumors are malignant. Sarcomas are the most common primary malignant tumors in the epididymis (Yu et al., 1992; Aydin et al., 2005). Primary adenocarcinoma of the epididymis has been reported but is exceedingly rare and demands work to distinguish from epididymal metastasis of clear cell renal cell carcinoma (RCC) (Yu et al., 1992; Kurihara et al., 1993; Jones et al., 1997; Aydin et al., 2005). We report a case of clear cell papillary cytadenocarcinoma of the epididymis. An immunohistochemical study of immunohistochemical markers for RCC was conducted to distinguish this tumor from metastatic clear cell RCC.

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Materials and methods

Case report

A 70-year-old man presented with a painless scrotal mass on the left side. The patient had noticed left-side scrotal swelling for 40 years with gradual enlargement within the last year. On physiological examination, a left-side intrascrotal solid mass was palpated. Ultrasonographic examination revealed a left-side intrascrotal mass measuring 4x2.8x3 cm, with multilocular cysts (Fig. 1A). Ultrasonographic and CT scans detected no abnormal findings in other organs including lung, liver and kidney, except a simple renal cyst. Serum levels of lactate dehydrogenase, alpha-fetoprotein and beta-human chorionic gonadotropin were within normal limits. Under a diagnosis of left-side testicular tumor, a left-side orchiectomy was conducted through an inguinal approach. Macroscopically, the

scrotal mass was located adjacent to the testis. The cut surface showed that the entire scrotal mass consisted of two structures: a multiloculated cystic area and a solid yellow mass with foci of necrosis and hemorrhage (Fig. 1B). The testis was capsulated with a gray sheath, and measured 6.2x3.3x2.7 cm.

Methods

Tumor tissue obtained from orchiectomy were fixed in 10% formalin and embedded in paraffin. One-micrometer sections were stained with hematoxylin-eosin, and were used for immunohistochemical studies. Immunohistochemical expression of markers for RCC was examined using the following antibodies: RCC marker (Dako), CD10 (Dako), vimentin (Dako), carbonic anhydrase IX (CAIX) (Abcam), glutathione S-transferase α (GST-α) (Novocastra), PAX2 (Invitrogen), α-methylacyl-CoA racemase (AMACR) (Thermo), vinculin (Calbiochem), cytokeratin-7 (CK7) (Dako), and C-KIT (Dako). Immunohistochemical examination was conducted according to a previously reported protocol (Konda et al., 2008). Antigen retrieval was done except for GST-α.

Results

The tumor showed heterogeneous histology. Most notably, there were areas that resemble clear cell RCC. Tumor cells with small round nuclei and abundant clear

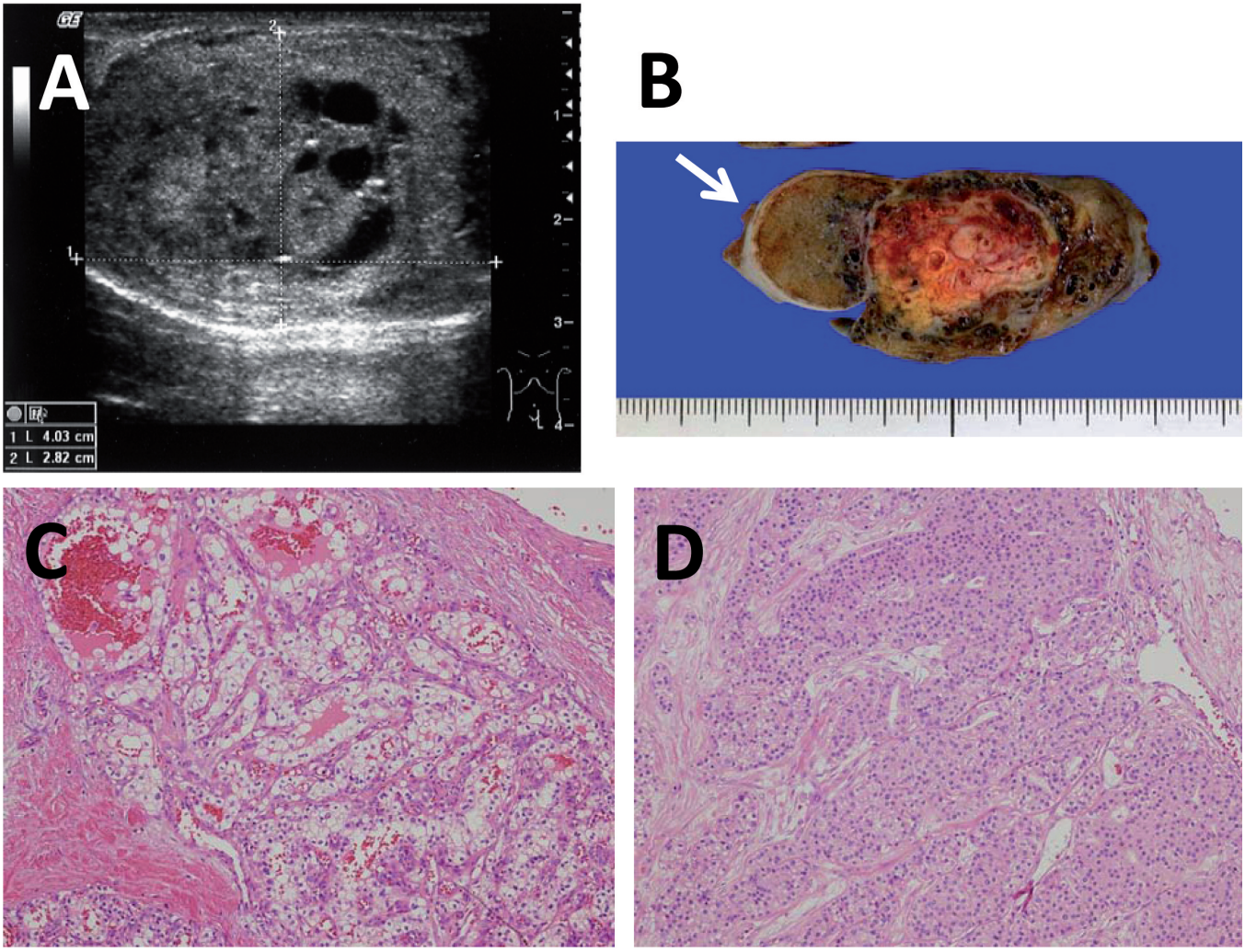

Fig. 1. A case of clear cell papillary cystadenocarcinoma of the epididymis. **A.** Ultrasonography shows an intrascrotal solid tumor with multiloculated cystic deformity. **B.** The cut surface of the resected tumor shows that the tumor consists of two structures: a multiloculated cystic area and a solid yellow mass with foci of necrosis and hemorrhage. Arrow indicates testis. **C.** The area that resembles clear cell RCC. Tumor cells with small round nuclei and abundant clear cytoplasm form solid nests and tubular structure. **D.** The tumor around foci of necrosis. The tumor cells have eosinophilic cytoplasm displaying nuclear atypia and occasional mitotic figures. C, D, Hematoxilin and eosin (H&E), x 200.

cytoplasm form solid nests and tubular structure (Fig. 1C). In contrast, tumor cells around foci of necrosis had clear to eosinophilic cytoplasm and displayed nuclear atypia and occasional mitotic figures (Fig. 1D). Invasion to adjacent testicular capsule and surrounding soft tissues was found. Since nuclear atypia, mitotic figures, necrosis and invasion to surrounding structures are absent in clear cell papillary cystadenoma of the epididymis, we diagnosed this tumor as clear cell papillary cystadenocarcinoma of the epididymis (Odrzywolski and Mukhopadhyay, 2010).

The results of immunohistochemistry are summarized in Table 1. In the present case, tumor cells were diffusely positive for vimentin, CAIX, CK7 and PAX2 (Fig. 2A-D). In contrast, no immunoreactivities for RCC marker, GST-α (Fig. 2E), AMACR, vinculin or C-KIT were detected. CD10 was expressed in tumor cells with eosinophilic cytoplasm located around the foci of necrosis, but not in those with clear cytoplasm (Fig. 2F).

Discussion

Epithelial neoplasmas of the testicular adnexal structure are rare and usually of mesenchymal origin, with the exception of cystadenomas of the epididymis (Yu et al., 1992; Jones et al., 1997; Aydin et al., 2005; Richie and Steele, 2007; Odrzywolski and Mukhopadhyay, 2010). Clear cell papillary cystadenoma is a rare benign epithelial tumor of the epididymis, comprising only 4% of all epididymal tumors. Only 59 histologically proven cases have been reported in the English-language literature (Odrzywolski and Mukhopadhyay, 2010). Clear cell papillary cystadenoma of the epididymis may present as a sporadic tumor or as a component of Hippel-Lindau's disease (Odrzywolski and Mukhopadhyay, 2010). When bilateral, the likelihood of association with Hippel-Lindau's disease is high. In contrast, there are few reports documenting adenocarcinoma of the epididymis (Yu et al., 1992; Kurihara, et al. 1993; Jones et al., 1997). Nuclear atypia, mitoses, necrosis and invasion of surrounding structure are absent in clear cell papillary cystadenoma of the epididymis (Odrzywolski and Mukhopadhyay, 2010). In the present case, the tumor cells displayed nuclear atypia and mitoses. Foci of necrosis and invasion to adjacent testicular capsule and surrounding soft tissues were observed. From these observations, together with the negative findings in other organs, including kidney on CT and ultrasonographic examinations, we diagnosed this tumor as clear cell papillary cystadenocarcinoma of the epididymis. Clear cell cystadenoma of the epididymis is associated with von Hippel-Lindau disease in approximately two-thirds of cases, whereas none of the reported cases of clear cell cystadenocarcinoma of the epididymis, including the present case, had a history of von Hippel-Lindau disease (Yu et al., 1992; Kurihara et al., 1993; Jones et al., 1997; Odrzywolski and Mukhopadhyay, 2010).

Clear cell cystadenocarcinoma of the epididymis must be distinguished from other tumors presenting as a scrotal mass with or without hydrocele, which arise in the testis, testicular adnexa and paratesticular structures. The candidate differential diagnoses include testicular lymphoma, adenomatoid tumor, mesothelioma, serous papillary carcinoma, carcinoma of the rete testis, and sarcomas (Jones et al., 1997; Richie and Steele, 2007). Since clear cell papillary cystadenocarcinoma of the epididymis is histologically characterized by tubular or tubulopapillary growth and the presence of cuboidal or columnar cells with water-clear cytoplasm, and is localized in the epididymis, a preliminary diagnosis is not necessarily difficult (Jones et al., 1997; Richie and Steele, 2007). However, the histological features of clear cell papillary cystadenoma or cystadenocarcinoma of the epididymis resemble metastatic clear cell RCC.

Table 1. Immunohistochemical Profiles of Clear Cell Papillary Cystadenocarcinoma of the Epididymis (CCPCCE), Clear Cell Papillary Cystadenoma of the Epididymis (CCPCE), Clear Cell Renal Cell Carcinoma (CC-RCC) and Clear Cell Papillary RCC (CCP-RCC).

	CCPCCE (this case)	CCPCE (ref. no. 1, 2)	CC-RCC (ref. no.3-5)	CCP-RCC (ref. no. 6-8)
RCC marker	negative	negative	positive	negative
CD10	positive*	negative	positive	negative
GST-α	negative	-	positive	-
Vimentin	positive	positive	positive	-
CAIX	positive	-	positive	positive
PAX2	positive	positive	positive	positive
AMACR	negative	-	negative	negative
Vinculin	negative	-	negative	negative
CK7	positive	positive	negative	positive
C-KIT	negative	-	negative	-

*Positive in tumor cells with eosinophilic cytoplasm. In the cases of CCPCE, CC-RCC and CCP-RCC, typical immunohistochemical profiles are shown. RCC; renal clear cell, GST-α; glutathione S-transferase α, CAIX; carbonic anhydrase IX, AMACR; α-methylacyl-CoA racemase, CK7; cytokeratin-7. Ref. 1. Aydin et al., 2005; 2. Odrzywolski and Mukhopadhyay, 2010; 3.Gokden et al., 2008; 4. Martignoni et al., 2007; 5 Ozcan et al., 2009; 6. Gobbo et al., 2008; 7. Kuroda et al., 2008; 8. Tickoo et al., 2006.

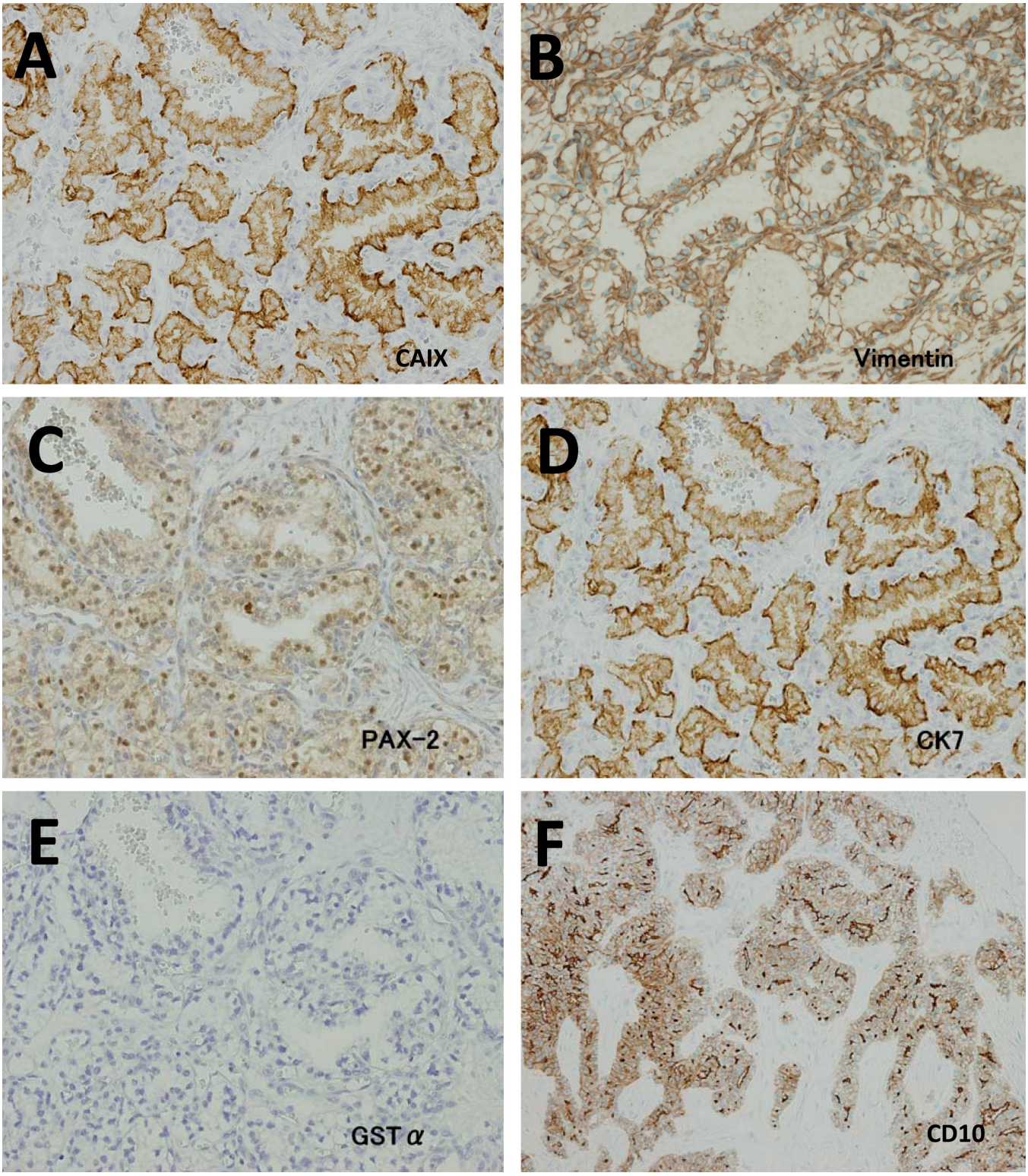

Fig. 2. Immunohistochemical markers for RCC. Immunohistochemical staining shows immunoreactivities to CAIX **(A)**, vimentin **(B)**, PAX-2 **(C)** and CK7 **(D)**, and no reactivity to GST-α **(E)**. Positive immunostaining for CD10 is observed in the areas occupied by tumor cells with eosinophilic cytoplasm **(F)** x 200.

Therefore, it is obligatory to distinguish the two epididymal tumors from metastatic clear cell RCC. Previous immunohistochemistry used molecular markers for RCC, including RCC marker, CD10 and CK7 to differentiate between clear cell papillary cystadenoma and clear cell RCC (Aydin et al., 2005; Odrzywolski and Mukhopadhyay, 2010). Since most of the papillary cystadenomas of the epididymis display positive immunostaining for cytokeratin 7 and negative staining for RCC marker and CD10, these 3 markers have been suggested to be useful immunohistochemical features to distinguish papillary cystadenoma of the epididymis from metastatic clear cell RCC. However, there is no report on immunohistochemical studies of RCC markers for the differentiation between clear cell papillary adenocarcinoma of the epididymis and clear cell RCC. In the present study, we examined ten immunohistochemical markers for RCC as shown in Table 1 (Martignoni et al., 2007; Gokden et al., 2008; Ozcan et al., 2009). The present case displayed diffuse immunoreactivities to PAX2, CAIX, vimentin, and CK7, and focal immunoreactivity to CD10 (Table 1). Papillary cystadenoma of the epididymis was reported to show positive immunostaining for PAX2 (Odrzywolski and Mukhopadhyay, 2010), although we found no information concerning the expression of GST-α, AMACR, vinculin and C-KIT. PAX2 is essential for the development of the Wolffian ducts, and is expressed in male genital tract including epididymis (Tong et al., 2011). Expression of PAX2 in primary epithelial neoplasms of the male genital tract is considered to be due to their histogenetic relationship with Wolffian ducts. Clear cell RCC usually show positive staining for RCC marker, CD10, GST-α, PAX2, CAIX and vimentin. In contrast, immunoreactivities to CK7, AMACR, C-KIT and vinculin are scarcely observed in clear cell RCC. From these observations, it is not necessarily difficult to distinguish between clear cell cystadenocarcinoma of the epididymis and metastatic clear cell RCC. However, the histopathologic and immunohistochemical features in the present case resembled clear cell papillary RCC, which is a tumor composed predominantly of cells with clear cytoplasm arranged in cystic and papillary pattern, displaying positive immunostaining for CK7, CAIX and PAX2; mostly negative for vinculin; and negative for CD10, RCC marker and AMACR (Tickoo et al., 2006; Gobbo et al., 2008; Kuroda et al., 2011). Although most of the clear cell papillary RCC arise in kidneys with end-stage renal disease, this tumor may occur in otherwise normal kidneys as sporadic RCC (Gobbo et al., 2008). In the present case, we cannot rule out epididymal metastasis of RCC, even though immunohistochemical expression of markers for RCC is definitely different from that of clear cell RCC. Considering the long disease history in the reported cases, including the present case, it is conceivable that clear cell papillary adenocarcinoma of the epididymis is a low-grade malignancy with slow progression or malignant transformation from cystadenoma (Yu et al., 1992; Kurihara et al., 1993; Jones et al., 1997). There are two reports of transformation from cystadenoma to cystadenocarcinoma (Odrzywolski and Mukhopadhyay, 2010).

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