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Chlamydial endometritis

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SUMMARY Endometrial biopsies were obtained from 32 women with suspected pelvic inflammatory disease, of whom 23 (72%) had histopathological evidence of endometritis. *Chlamydia trachomatis* was isolated from the endometria of nine (39%) women (chlamydia group) but not from the other 14 (non-chlamydia group). Severe plasma cell endometritis and lymphoid follicles with transformed lymphocytes were significantly more common in the chlamydia group than in the non-chlamydia group. This suggests that *C trachomatis* is an invasive endometrial pathogen which often causes severe inflammation. The association was independent of predisposing factors such as use of intrauterine contraceptive devices.

Chlamydia trachomatis is the most important cause of acute pelvic inflammatory disease.[1] Cervical chlamydial infection ascends intraluminally to the upper genital tract, the endometrium, and fallopian tubes.[2,3] *C trachomatis* has been directly isolated from the fallopian tubes of women with acute salpingitis.[1] Endometritis as an intermediate state of such ascending chlamydial infection has been little studied, and only a few cases of *C trachomatis* associated endometritis have been reported.[4–8] Thus the histopathological characteristics of this infection are largely unknown. We have investigated the histopathological manifestations of chlamydial and non-chlamydial endometritis associated with pelvic inflammatory disease.

Material and methods

STUDY POPULATION

The study population consisted of 32 women seen consecutively as part of an ongoing study of acute pelvic inflammatory disease at the Department of Obstetrics and Gynaecology, University Central Hospital, Tampere, Finland. Women who had taken antibiotics or those who had undergone gynaecological operations or any investigations of the upper genital tract within the previous month were excluded from the study. Patients were evaluated as previously described.[9] All patients underwent laparoscopy and endometrial biopsy after the nature of the procedures had been fully explained and informed consent obtained.

COLLECTION OF SPECIMENS

Specimens for isolation of *C trachomatis, Neisseria gonorrhoeae, Mycoplasma hominis, Urea plasma urealyticum,* herpes simplex virus, and facultative and anaerobic bacteria were obtained from the cervix, endometrium, fallopian tubes, and cul de sac as described previously.[10] Endometrial specimens were obtained during general anaesthesia by transcervical aspiration. The cervix was first wiped carefully and a sterile disposable fertility cannula (Pro-Ception, Milex Co, USA) was inserted into the endocervical canal through the internal os. When the catheter was in place, the stylet was removed, and a disposable baby feeding catheter was inserted through the cannula beyond the internal os until it touched the uterine fundus. A 10 ml syringe was then attached to the catheter and endometrial material was aspirated for isolation of the micro-organisms. A single strip endometrial biopsy specimen was obtained transcervically using a disposable Vabra (Ferrosan Co, Denmark) endometrial suction curette equipped with a 3 mm metallic tip. The biopsy specimens were fixed in 10% buffered formalin and processed by routine histological methods, including staining

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by the method of Herovici.[11] Haematoxylin and eosin, Giemsa, and methyl green pyronin[12] stainings were also used. Deeper parts of endometrium were inadequate in four biopsies. In one case the endometrial biopsy specimen was too small for evaluation of all the histopathological variables used. This patient was excluded from further analysis.

MICROBIOLOGICAL STUDIES

C trachomatis was isolated using cycloheximide treated McCoy cells[13] and the inclusion bodies were visualised by iodine. Cultures for *N gonorrhoeae* were performed by inoculation of the swabs, initially transported in Stuart's media, on to Thayer-Martin agar plates. Oxidase positive colonies were identified as *N gonorrhoeae* by an immunofluorescence technique using fluorescein isothiocyanate conjugated rabbit anti-*N gonorrhoeae* antibodies (Difco, USA).[14] Specimens for culture of *M hominis* and *U urealyticum* were inoculated into SP-4[15] and 10-B[16] media respectively. Subcultures for identification of *M hominis* were performed on SP-4 plates, and positive isolation was verified by a growth inhibition test using discs impregnated with antiserum.[17] Specimens for culture of *U urealyticum* were subcultured on differential agar medium A7 and identified as described previously.[18] Port-A-C specimens for isolation of facultative and anaerobic bacteria were handled as described elsewhere.[10] Specimens for isolation of herpes simplex virus were placed in viral transport media (Virocult, Orion Diagnostica, Finland) and inoculated on to human embryonic fibroblast monolayers.[20]

HISTOPATHOLOGICAL METHODS

The biopsy specimens were reviewed by one of us without knowledge of any clinical or microbiological findings. Standard terms of evaluating histopathological and cellular findings were used.

The histopathological diagnosis of endometritis was based on identification of plasma cells.[21,22] In all cases the presence of plasma cells was confirmed with methyl green pyronin staining. The average number of plasma cells was quantitated as 1+ to 3+ according to the following scheme: 1+ when fewer than 20 plasma cells were seen per high power field in at least five fields (1+ plasma cells were usually seen in superficial parts of the functional endometrium); 2+ when 20 to 60 plasma cells were seen per high power field; and 3+ when more than 60 plasma cells were seen per high power field. Dense infiltrations of lymphocytes—that is, lymphoid follicles—were recorded as present or absent. Lymphoid follicles were defined as rounded follicular accumulations of large transformed lymphocytes. They were usually surrounded by dense inflammatory infiltrates of plasma cells. The number of polymorphonuclear leucocytes was quantitated as follows: 1+ when a few were present focally in the superficial parts of endometrium; 2+ when diffuse infiltrations and focal collections were seen; and 3+ when larger collections and confluent infiltrations were present all over the specimen. The presence or absence of focal polymorphonuclear leucocyte infiltrations of endometrial glands (microabscesses), tissue oedema, haemorrhagia, necrosis, and fibrosis was also recorded.

Endometritis was classified into mild, moderate, and severe. This was based mainly on the number of plasma cells present, but attention was also paid to associated inflammatory abnormalities in the functional endometrium. In mild endometritis the inflammatory infiltrate was slight and scattered in

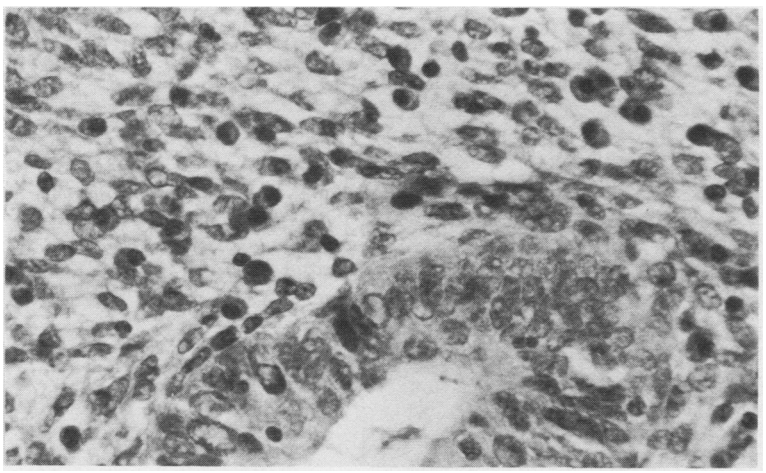

Fig. 1 *Mild endometritis with slight diffuse plasma cell infiltration. Haematoxylin and eosin.* × *132.*

the superficial part of oedematous endometrial stroma (Fig. 1) Only focal aggregates of plasma cells were seen. In moderate endometritis more pronounced infiltrations of plasma cells were seen throughout the specimen (Fig. 2). Lymphocytes and plasma cells were also found in larger focus like aggregates, which sometimes became confluent. The density of the endometrial stroma was more prominent than in mild endometritis. Endometritis was considered severe when pronounced diffuse infiltrations of plasma cells were seen all over the biopsy specimen replacing the endometrial stroma (Fig. 3). Besides plasma cells, other inflammatory cells were more abundant. Infiltration of endometrial glands by polymorphonuclear leucocytes was more prominent than in moderate endometritis. Lymphoid follicular structures were often present within the inflammatory stromal infiltrate. Because of severe inflammatory changes histopathological dating of the endometrium was often impossible.

STATISTICAL ANALYSIS

Analysis of variance, Fisher's exact test, and χ^2 test, where appropriate, were used for statistical analyses.

Results

PREVALENCE OF ENDOMETRITIS

Endometrial biopsy showed endometritis in 23 (72%) of the 32 women with suspected pelvic inflammatory disease. Of those 23 women with pathological evidence of endometritis, 19 (83%) had salpingitis at laparoscopy and four (17%) did

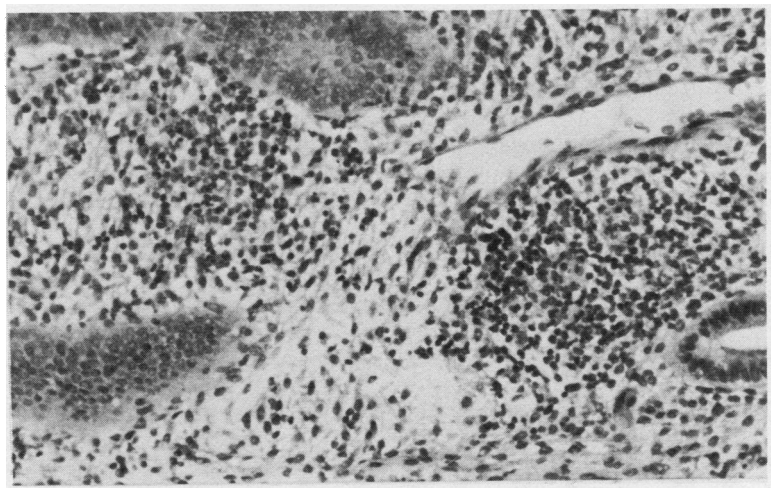

Fig. 2 *Moderate endometritis with confluent focus like aggregates of inflammatory cells. Haematoxylin and eosin.* × *66.*

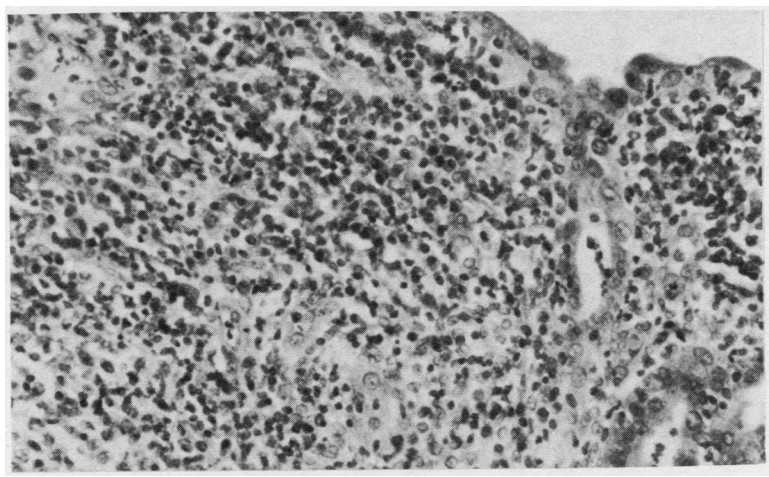

Fig. 3 *Severe endometritis with pronounced plasma cell infiltration. Haematoxylin and eosin.* × *66.*

not. Endometritis was mild in six (26%) cases, moderate in six (26%) cases, and severe in 11 (48%) cases. Table 1 shows the correlation of histological findings with selected demographic and clinical findings. There were more women with moderate and severe endometritis using intrauterine contraceptive devices than those with mild endometritis and they also had longer histories of symptoms. There was a significant correlation between the severity of endometritis and the acute phase erythrocyte sedimentation rate.

ISOLATION OF SPECIFIC MICRO-ORGANISMS FROM THE ENDOMETRIUM

C trachomatis was the most prevalent organism: it was isolated from the endometrium of nine women and from the cervix of 10. Three women had *C trachomatis* isolated from the cervix but not from the endometrium, and two women had *C trachomatis* isolated from the endometrium but not from the cervix. Three women had *C trachomatis* isolated from the cervix, endometrium, and fallopian tubes. *C trachomatis* was the only organism isolated from the endometrium in three cases, and in six cases other organisms were isolated as well (Table 2).

N gonorrhoeae was isolated from the endometrium in three cases, *M hominis* in four cases, *U urealyticum* in three cases, herpes simplex virus type 2 in one case, facultative bacteria (including *Streptococcus α-haemolyticus,* group B streptococcus, *Staphylococcus aureus, Haemophilus influenzae*) in six cases, and anaerobic bacteria (including *Peptostreptococcus* spp, *Bacteroides bivius,* and *B melaninogenicus*) in seven cases. Since *C trachomatis* was the most prevalent organism isolated we divided the cases into two groups according to whether or not *C trachomatis* was isolated from the endometrium (Table 2). There was no correlation of the isolation of *C trachomatis* with the isolation of other specific micro-organisms from the endometrium (Table 2). None in the chlamydia group had mycoplasmas isolated.

CORRELATION OF HISTOPATHOLOGICAL CHARACTERISTICS OF ENDOMETRITIS WITH THE ISOLATION OF *C TRACHOMATIS*

Table 3 shows that severe endometritis was significantly associated with the isolation of *C trachomatis*. Thus seven (87%) of the eight women who had *C trachomatis* isolated from the endometrium showed severe endometritis compared with only four (29%) of the 14 women who did not have *C trachomatis* isolated from the endometrium ($p = 0.023$) (one of the four women with severe endometritis in the latter group had *C trachomatis* isolated from the cervix). After adjusting for the

Table 1 *Correlation of histopathological findings with selected demographic and clinical findings in 23 women with endometritis*

Finding	*Severity of endometritis*			
	Mild (n = 6)	*Moderate (n = 6)*	*Severe (n = 11)*	
Age (yr)*	23 (4)	25 (9)	27 (8)	
Method of birth control (no (%))				
Birth control pills	2 (33)	0 (—)	1 (9)	†
Intrauterine contraceptive device	0 (—)	4 (67)	5 (45)	†
Other	3 (50)	0 (—)	5 (45)	†
None	1 (17)	2 (33)	0 (—)	†
Duration of symptoms (days)*	2·2 (1·0)	10·8 (11·5)	10·5 (7·9)	
Temperature on admission (°C)*	37·7 (0·9)	37·5 (0·8)	37·2 (0·7)	
Erythrocyte sedimentation rate (mm in the first hour)*	17 (10)	31 (22)	52 (18)	‡
C reactive protein concentration (mg/l)*	48 (52)	57 (69)	69 (34)	

*Values given as mean (standard deviation).
†$p = 0.049$ (χ^2 test).
‡$p = 0.0027$ (analysis of variance).

Table 2 *Correlation of the isolation of Chlamydia trachomatis with the isolation of other micro-organisms from the endometrial cavities of 23 women with plasma cell endometritis*

Micro-organism	*C trachomatis isolated (n = 9)*	*C trachomatis not isolated (n = 14)*	*Total (n = 23)*
Neisseria gonorrhoeae	1 (11)	2 (14)	3 (13)
Mycoplasma hominis	0	4 (29)	4 (17)
Urea plasma urealyticum	0	3 (21)	3 (13)
Herpes simplex virus type 2	1 (11)	0	1 (4)
Facultative bacteria	2 (22)	4 (29)	6 (26)
Anaerobic bacteria	4 (44)	4 (29)	8 (35)

Values given as number (%) of women.

presence or absence of an intrauterine contraceptive device, the association between pathological evidence of severe endometritis and the isolation of *C trachomatis* from the endometrium was even more pronounced ($p = 0{\cdot}0013$) among those women who were not using intrauterine contraceptive devices.

The histopathological picture of severe endometritis was characterised by pronounced diffuse inflammatory infiltrates of plasma cells, and lymphocytes were seen in the endometrial stroma throughout the biopsy specimen. Lymphoid follicles with transformed lymphocytes were seen in six (75%) of the eight patients who had positive endometrial cultures for *C trachomatis* (one case with a relatively small biopsy specimen showed severe inflammation but follicular structures were not seen) compared with none of those without *C trachomatis* isolated from the endometrium ($p = 0{\cdot}0004$). In three cases the lymphoid follicles were small and in three cases medium sized or large. The cells comprising these lymphoid follicles were large or medium sized transformed lymphocytes with abundant pyronin positivity in the cytoplasm. Starry sky phagocytes were seen infrequently. Dense infiltrations of plasma cells was usually seen in the periphery of these lymphoid follicles. Fig. 4 shows a typical lymphoid follicle. No correlation was found between the presence of polymorphonuclear leucocytes and the isolation of *C trachomatis* (Table 2). One patient with chlamydial endometritis had small numbers of eosinophils.

Other inflammatory changes such as cytoplasmic eosinophilia and squamous metaplasia of the surface epithelium, as well as focal inflammatory infiltrations of the endometrial glands (microabscesses), were more common in severe endometritis, but no significant differences were found between cases with or without *C trachomatis*. Intracytoplasmic inclusions in swollen epithelial cells were seen in one case with *C trachomatis* isolated from the endometrium.

Fibrous tissue was seen in two (25%) cases in which *C trachomatis* was isolated from the endometrium and in four (29%) cases in which *C trachomatis* was not isolated. One of the latter four women had *C trachomatis* isolated from the cervix.

Neither of the two women with *N gonorrhoeae* isolated from the endometrium had lymphoid follicles present. One had moderate superficial endometritis with 2+ plasma cells, and the other had mild diffuse endometritis with 1+ plasma cells.

Epitheloid cell granulomas with necrosis and giant cells of Langhans' type were not seen in any of the specimens.

Discussion

Endometritis is often an obscure entity to pathologists, although it is commonly seen in uterine curettings obtained after abortion and parturition.[23] Furthermore, histopathological studies among infertile patients have shown that endometritis is not an uncommon finding.[21 24] The presence of plasma cells within the endometrium is generally accepted as a histopathological definition of endometritis.[22 23] The presence of polymorphonuclear leucocytes and lymphocytes are not included because they can also be found during the normal menstrual cycle.

In this study histopathological evidence of endometritis was found in 72% of 32 patients refer-

Table 3 *Correlation of selected histopathological characteristics of endometritis with the isolation of Chlamydia trachomatis from the endometrium*

Characteristics of endometritis	*C trachomatis isolated (n = 8)*	*C trachomatis not isolated (n = 14)*	*p*
Severity			
Mild	0	6 (42)	
Moderate	1 (13)	4 (29)	0·023
Severe	7 (87)	4 (29)	
Lymphoid follicles with transformed lymphocytes	6 (75)	0	0·0004
Plasma cells			
+	0	5 (36)	
++	5 (62)	6 (43)	NS*
+++	3 (38)	3 (21)	
Polymorphonuclear leucocytes			
+	5 (62)	3 (21)†	
++	2 (25)	5 (36)	NS
+++	1 (13)	1 (7)	
Polymorphonuclear leucocytes in endometrial glands (microabscesses)	3 (38)	3 (21)	NS
Fibrosis	2 (25)	4 (29)	NS
Oedema	2 (25)	4 (29)	NS
Necrosis	2 (25)	3 (21)	NS
Haemorrhagia	5 (62)	14 (100)	NS
Intracytoplasmic inclusions	1 (13)	0	NS

*NS = not significant.
†Not seen in five patients (36%).
Values given as number (%) of women.

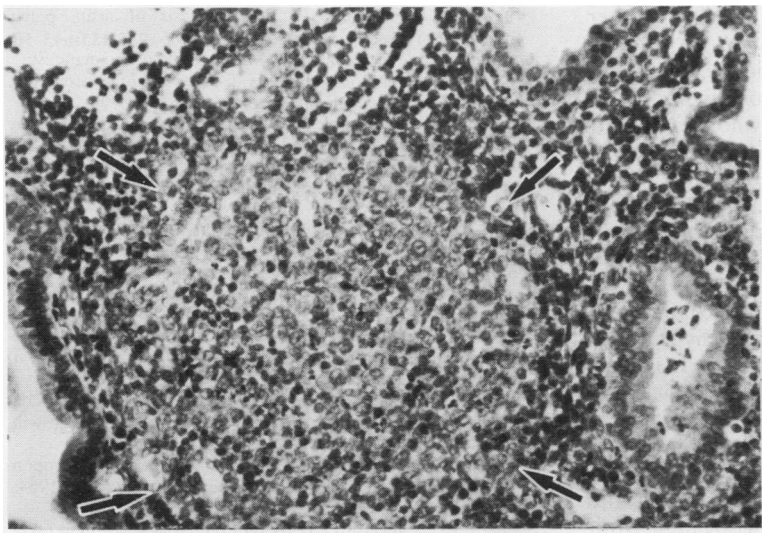

Fig. 4 *Follicular lymphoid infiltrate comprising transformed lymphocytes. Note the demarcations which are quite indistinct (arrows). Haematoxylin and eosin.* × *66.*

red for acute pelvic inflammatory disease. This prevalence is relatively high and supports the concept that endometritis is associated with non-puerperal pelvic inflammatory disease. Furthermore, it is in agreement with a recent related study which showed pathological evidence of endometritis in 40% of 35 patients with mucopurulent cervicitis who did not have frank pelvic inflammatory disease.[2] These results suggest that the pathogenesis of acute salpingitis entails intraluminal spread of infection from the cervix via the endometrium to the fallopian tubes.

We found that *C trachomatis* was the most prevalent (39%) micro-organism isolated from the endometrium. A previous study by Stray-Pedersen *et al*[24] implicated mycoplasmas in the aetiology of endometritis, but they did not control for *C trachomatis*. In the present study none in the chlamydia group had mycoplasmas isolated, whereas in the non-chlamydia group *U urealyticum* was isolated from three women and *M hominis* was isolated from four. Since *C trachomatis* was the most prevalent organism isolated and there were no significant differences between those with and those without *C trachomatis* in the presence of other micro-organisms, it is conceivable that the histopathological differences observed between the two groups were caused by *C trachomatis* and not by other organisms.

We isolated *N gonorrhoeae* from the endometrium in three cases only (one patient had *C trachomatis* isolated as well). One patient with gonococcal endometritis had mild and the other patient had moderate endometritis. Because of the relatively small number of patients studied and the low isolation rate of *N gonorrhoeae,* we cannot exclude the possibility that some of the histopathological findings we described might be caused by *N gonorrhoeae* as well. On the other hand, gonococcal endometritis is usually milder and transient, and lymphocytic response with transformed lymphocytes has not been described.[25] Gonococcal endometritis and endometritis caused by facultative and anaerobic bacteria may be limited to the superficial mucosal surface, whereas *C trachomatis* may cause deeper endometrial infection. In this study tuberculous endometritis was easily excluded by the absence of typical epitheloid cell granulomas surrounded by lymphocytic infiltrations.

We found that severe endometritis and lymphoid follicles comprising transformed lymphocytes were significantly more common in the chlamydial endometritis group than in the non-chlamydial endometritis group, which suggests that *C trachomatis* is an invasive endometrial pathogen. Not unexpectedly, use of an intrauterine contraceptive device was also associated with the severity of endometritis. After excluding women using these devices, however, the difference between the two groups remained significant. We also found that the presence of microabscesses was more common among those with chlamydial infection (38% *v* 21%). Interestingly, some of these findings, such as severe inflammation with active lymphoid follicles, are close to those described in chlamydial eye infection (trachoma) and chlamydial cervicitis.[26–30]

Previous studies have described severe endometritis associated with *C trachomatis* in a limited number of cases[4–8] but no uniform criteria have been used and no detailed histopathological description of the infection has been given. Furthermore,

the presence or absence of micro-organisms other than *C trachomatis* has generally not been studied. In one recent study[8] histopathological examination showed pronounced inflammation of the endometrium in four of eight patients from whom endometrial biopsies were obtained. Endometrial cultures of two of the four patients were positive for *C trachomatis*. Möller *et al*[7] reported one case with "follicular lymphoid endometritis" probably representing a morphological finding similar to that described in our study.

Further studies are now warranted to characterise in detail the nature of the lymphoid hyperplasia associated with chlamydial endometritis. It is conceivable that the lymphoid hyperplasia indicates a strong B cell activation caused by *C trachomatis*. In vitro *C trachomatis* stimulates human peripheral blood B lymphocytes to proliferate and secrete polyclonal immunoglobulins.[31] In vivo, however, the immunopathological phenomena associated with chlamydial pelvic inflammatory disease are as yet largely unknown. Genital infections caused by *C trachomatis* have been recognised as a major public health problem with serious sequelae in women such as infertility and pregnancy associated morbidity. Clinically unrecognised endometritis and salpingitis undoubtedly occur among women with "asymptomatic" chlamydial infection since less than half of the women with tubal infertility have a history of frank pelvic inflammatory disease.[32]

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