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Extrauterine Malignancies Detected on Papanicolaou Smear: The Clinical and Cytomorphological features of Eight Patients

Papanicolaou Smear'da Saptanan Rahim Dışı Maligniteler: Sekiz Hastanın Klinik ve Sitomorfolojik Özellikleri

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ÖZ

Amaç: Papanicolau smear (Pap), serviks kanseri tanısında etkili bir tekniktir. Bu muayenede atipik glandüler hücreler ortaya çıkabilir ve bazen ekstratuerin malignitenin ilk belirtisi olabilir. Bu çalışmada sunulan 8 vaka, tümü klasik Pap smear'larda tespit edilen, daha önce bilinmeyen ekstrauterin tümörlerin nadir görülen vakalarıdır

Metod: Klinik veri tabanının retrospektif analizi ile, standart Pap smear'da daha önce teşhis edilmemişrahim dışı tümörlerin bulunması amacıyla sitoloji arşivi ve hasta dosyaları taraması yapıldı.Taramada sekiz hasta bu kriterlerde bulundu. Bu hastaların hücre blokları ve sitomorfolojik incelemeleri tekraralanarak beraberinde klinik veriler incelendi.Bulgular: Pap smear tüm olgularda malignitenin ilk bulgusuydu. Hastalar asemptomatikti veya spesifik olmayan semptomları vardı. Kesin tanı yeterli radyolojik tetkik ve biyopsi sonrası konuldu. Sekiz vakanın tümü, histolojik olarak kanıtlanmış bir primer tümörün benzer sitomorfolojik özelliklerine sahipti. Atipik glandüler hücre grupları altı hastada en dikkat çekici bulguydu. Diğer iki hastada lenfatik kökenli hücreler ve atipik lenfositler saptandı. İmmünohistokimya ile hücre bloğu, üç vakada tanıyı net olarak doğruladı.

Sonuç: Pap smear kanser taraması için dünya çapında kabul gören bir yöntemdir. Rahim ağzı kanserleri için yüksek özgüllük ve duyarlılığa sahip olmasına rağmen, bu çalışmanın sonuçları, rutin taramalarda alınan Pap smear'ların titiz bir şekilde incelenmesinin asemptomatik hastalarda rahim dışı kanserleri de saptayabileceğini vurgulamaktadır.

Anahtar kelimeler: Papanicolaou Smear, Asemptomatik tarama, Malignite

ABSTRACT

Objective: Papanicolau smear (Pap) is an effective technique for the diagnosis of cervix cancer. Atypical glandular cells may be revealed in this examination and occasionally may be the first sign of extratuerine malignancy. The 8 cases presented in this study are uncommon cases of previously unknown extrauterine tumors all detected on classical Pap smears.

Study Design: A retrospective analysis of the clinical database identified eight women with previously undiagnosed extrauterine tumor detected on standard Pap smear. Clinical data were obtained from patient files and microscopic examination was repeated on the material obtained from the cytology archives. Cellblock and cytomorphology examinations were made, and clinical data were reviewed together with histopathology.

Results: Pap smear was the first sign of malignancy in all cases. The patients were asymptomatic or had non-specific symptoms. Definitive diagnosis was made after adequate radiological work up and biopsy. All eight cases had similar cytomorphological features of a histologically proven primary tumor. Atypical glandular cell groups were the most remarkable sign in six patients. In the other two patients, cells of lymphatic origin and atypical lymphocytes were detected. Cellblock with immunohistochemistry confirmed the diagnosis in three cases.

Conclusion: Pap smear is a worldwide accepted method for cancer screening. Although it has high specificity and sensitivity for cervical cancers, the results of this study highlight that rigorous examination of Pap smear.

Key words: Papanicolau smear, Malignancies, Asymptomatic screening

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INTRODUCTION

The Pap smear test was originally designed to detect premalignant cervical lesions and cancer, based on cytological examination of vaginal smear, and this test remains the gold standard as a low-cost, universal screening modality, especially in low-resource environments (1,2). Exfoliative cytology may also indicate the presence of malignancies other than cervical cancer(3). Malignant cells from extrauterine cancers can come from direct extension to the cervix or vagina in patients with known malignancies(4).

In very rare cases, atypical or malignant cells detected in a cervical smear can be the first manifestation of extrauterine malignancy (3). The most common primary sites being the ovaries, followed by the gastrointestinal tract, fallopian tubes and breasts (5). Data in literature demonstrate that extrauterine cancer detected from a Pap smear is very rare (2). However, advances in the smear examination techniques such as liquid-based cytology, molecular-based HPV genotyping, and analysis of immune markers, may increase the potential of Pap smear in detecting extrauterine cancers (6).

The aim of this study was to analyse the clinicopathological features of eight extrauterine cancers diagnosed from abnormal Pap smear tests as the first manifestation of a malignancy. The role of the cervicovaginal smear in the diagnosis and management of these malignancies was also discussed.

MATRIALS AND METHODS

This was a retrospective analysis of patients with extrauterine tumors diagnosed initially with conventional Papanicolaou smear. This research was conducted in Ankara Research and Training Hospital. From a search of the pathology archives of our institution, the data were retrieved of eight patients from 2015 to December 2021 including cytosmears and corresponding histopathological sections. Approximately ten thousand pap smear reports during this period were scanned. Patients who had been diagnosed with cervical and vaginal cancers and any previous cancer at the time of screening were excluded. Ethical clearance for the study was obtained from the Institutional Ethics Committee. The study only included patients diagnosed with extrauterine cancers with a routine Pap screening test. Positive pap smears of patients with a known malignancy were excluded.

The clinical records, operative reports and data from patient files were obtained. The Pap smears from all eight cases were reviewed, and a record made of patient age, site of primary neoplasm, extent and distribution of the tumor and metastases. Primary involvement of the uterus/cervix/vagina was ruled out with clinical and histopathological examinations in all cases. Histopathological reports of colposcopy-directed biopsies, cervical biopsies, cone biopsies, fractional curettage, and hysterectomies were reviewed for the presence of typical and atypical glandular cells.

All the Pap smears were obtained with a routine procedure. There were at least two smears prepared for each case, which were immediately fixed in methanol and stained using the standard Pap staining technique. Each smear was studied according to the 2001 Bethesda system. Immunohistochemistry studies were performed on paraffin-embedded tissue sections. Details of cytopathological features and clinical features are listed in Table 1.

RESULTS

The mean age of the eight patients was 59 years (range, 42– 75 years). None of the cases had a history of carcinoma at the time of the Pap smear evaluation. Pelvic pain, vaginal bleeding or spotting was the presenting symptom in two cases. The clinical details of the patients with primary sites of extrauterine cancers are listed in Table 1.

Table 1. Demographic and clinicopathologic features of the patients

No	Age	Complaint	Diagnosis	Stage	Treatment
1	68	None	Transitionel cell ca		Transurethral resection (TUR)
2	42	Pelvic pain	Tubal cancer	1a	TAH+BSO+BPPLND+Omentectomy
3	56	None	Ovarian cancer	1c	TAH+BSO+BPPLND+Omentectomy
4	65	None	Ovarian cancer	3b	TAH+BSO+BPPLND+Omentectomy
5	72	Abnormal bleeding	Ovarian cancer	3c	TAH+BSO+BPPLND+Omentectomy
6	75	None	Ovarian cancer	3c	TAH+BSO+BPPLND+Omentectomy
7	47	None	Lymphoma		Simple hysterectomy
8	48	None	Clear cell ca ovarian	1a	TAH+BSO+BPPLND+Omentectomy

Of the eight patients, six were asymptomatic. In the two patients with symptoms (Patients 2 and 5), the time interval between the onset of symptoms and detection of a positive Pap smear was 2 and 3 months, respectively.

The histological types of the various extrauterine carcinomas in the eight patients were as follows: ovarian adenocarcinoma; transitional cell carcinoma of bladder, tubal cancer, clear cell cancer of over and large cell lymphoma. Three of these eight cases had widespread disease but none of the patients had metastasis to the vagina or cervix. Two patients with ovarian papillary serous carcinoma had malignant effusion and one had ovarian carcinoma with involvement of both fallopian tubes and omentum. Total abdominal hysterectomy was the most common surgical treatment followed by radical hysterectomy. Six of the eight patients received chemotherapy.

Cytomorphological examinations showed clusters of atypical cells with prominent nucleoli, nuclear groove, nuclear membrane irregularity and scanty cytoplasm admixed with normal endocervical and squamous cells on a clear background. Cellular features such as prominent nucleoli and nuclear longitudinal groove suggest bladder origin (Figure 1a,b,c).

Figure 1: Cervical examination smear revealed a clean background, showing mature, normal cervical elements and numerous highly atypical, hyperchromatic, epithelial cells with large nuclei featuring palisading arrangement. (A: Papanicolaou, x200; arrows show atypical cells with hyperchromatic nucleus) (B: Papanicolaou, x400) (C:Transitional cell carcinoma of bladder (Bladder-TUR))

Figure 1A

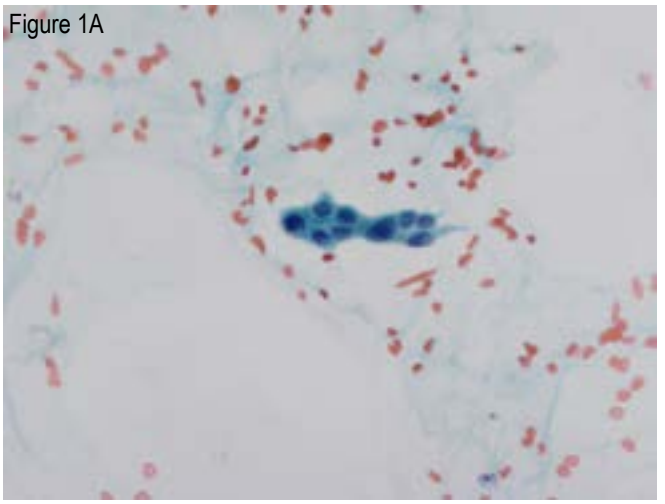


Figure 1B

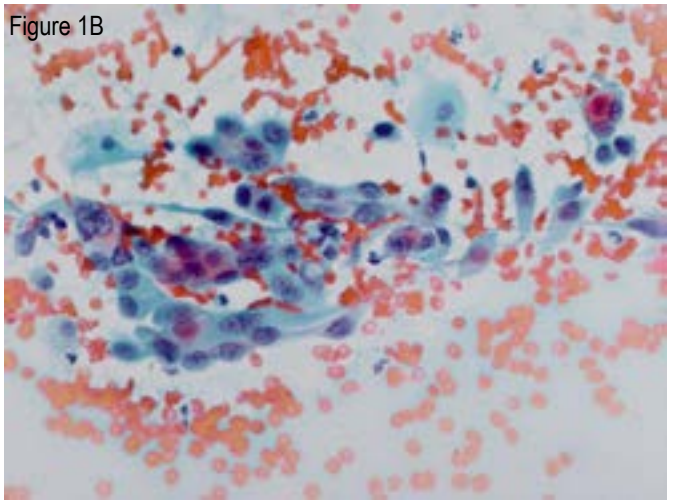
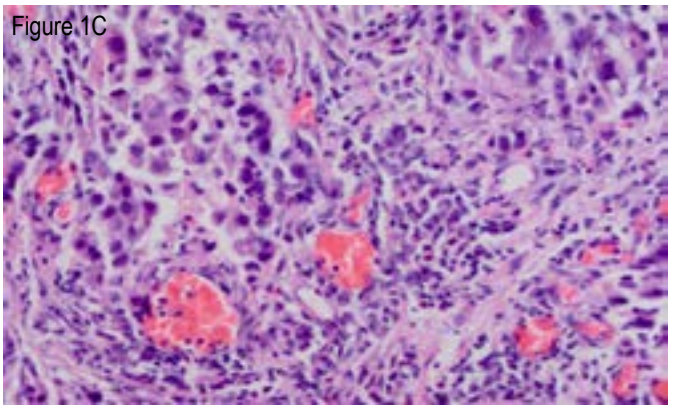


Figure 1C



The conventional Pap smear was atrophic backround in patient 8 with clear cell ovarian carcinoma. Some malignant cells with coarse chromatin, irregular nuclear membrane, vacuolar cytoplasm were noticed in the atrophic background (Figures 2a,b,c). The conventional Pap smear was atrophic backround in patient 8 with clear cell ovarian carcinoma. Some malignant cells with coarse chromatin, irregular nuclear membrane, vacuolar cytoplasm were noticed in the atrophic background (Figures 2a,b,c).

Fig. 2. Clear cell / Patient 8 A-B: Cervical smear examination demonstrating atypical cells of epithelial origin on a background of intermediary and parabasal cells together with neutrophils and leukocytes. (A: Papanicolaou, x500) C: Diffuse and strong CEA staining: Endometrial Biopsy

Figure 2A

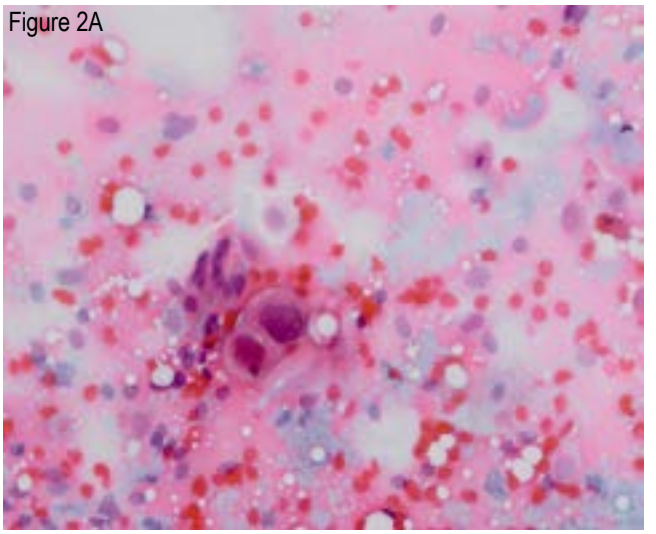
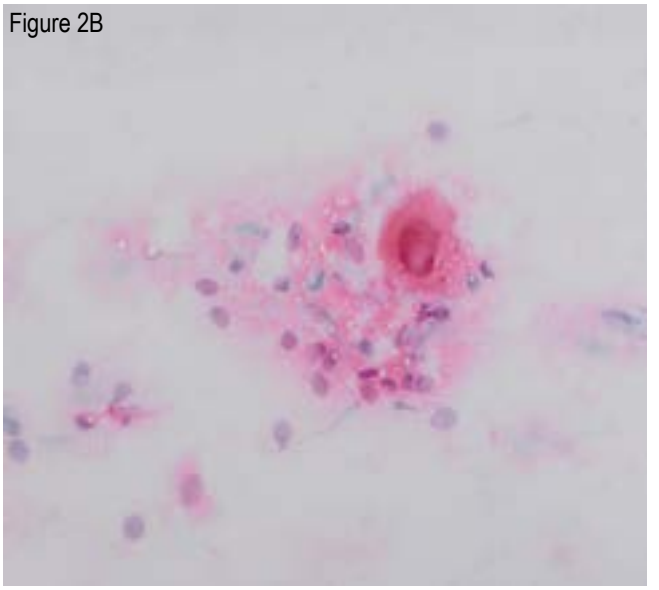
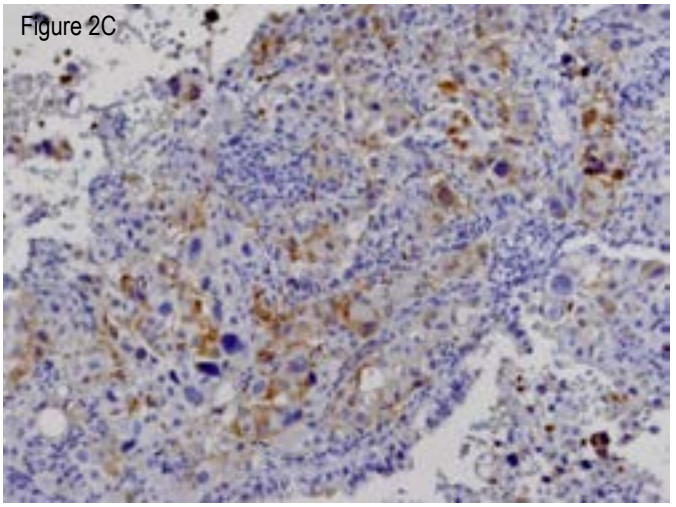


Figure 2B

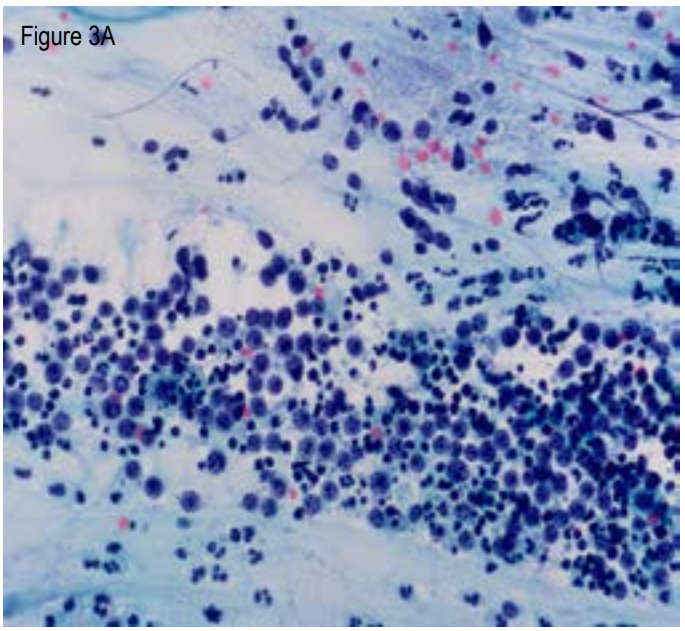


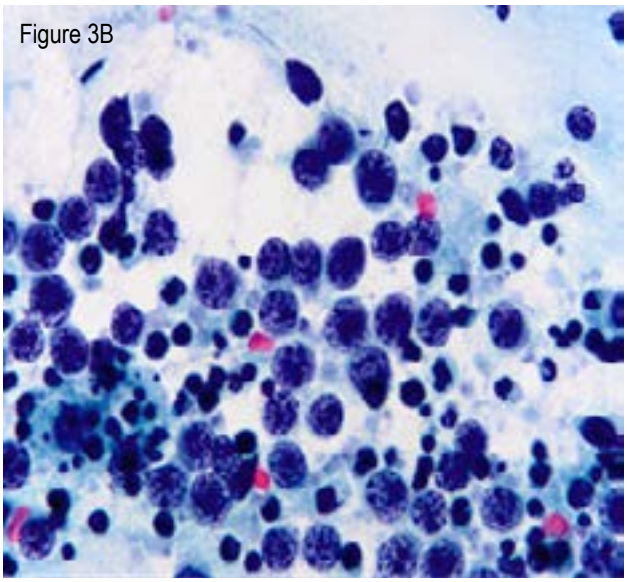


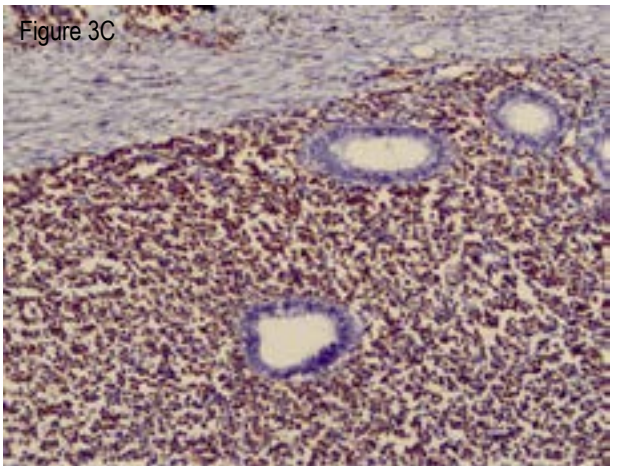
Epithelial cell abnormality, and atypical glandular cells, suggestive of endometrial or endocervical origin confirmed the diagnosis. Endometrial clear cell carcinoma diagnosis was made with endometrial biopsy. The Ki67 index was 80%. CEA was diffuse positive but vimentin, p53, MUC5ac, ER and progesterone were negative in the immunohistochemistry examination. But in this patient initial onset was ovarian origin.

Atypical appearing lymphoid cell groups admixed with normal squamous cells, endocervical cells and neutrophils were seen in a patient with lymphoma. The lymphoid cells were uniform, showing nuclear abnormalities including nuclear membrane irregularities and coarse uneven chromatin and several small nucleoli (Figure 3a,b,c).

Fig. 3. Lymphoma Patient 7 : Cervical examination smear showing atrophic background and groups of atypical cells of epithelial origin on a background of intermediary and parabasal cells together with neutrophils and leukocytes. (A-B: Papanicolaou, x500) C: Atypical lymphoid cells Show strong and diffuse immunreactivity for CD20 in curretage material.







After resection, microscopic examination demonstrated diffuse infiltration of the stroma and endometrial tissue by a monomorphic population of the malignant lymphoid cells Immunohistochemical studies showed that the neoplastic cells were only positive for B cell markers. A diagnosis of “Diffuse Large B cell non-Hodgkin’s Lymphoma” was made Most reports on extrauterine malignant tumors on routine Pap smears are single case reports (4,7,8,9). Most of the cases have a known history of extrauterine cancer and the appearance of malignant cells on a Pap smear is accepted as metastatic involvement (4,10). In one of the largest published reports, Gupta et al reviewed approximately 900,000 smears in a period of more than 20 years and detected only 33 (0.004%) cases with extrauterine cancer. The vast majority had a history of cancer at the time of the abnormal Pap smear (85%) (4). Although extremely rare, malignant cells in a cervical smear may be the first manifestation of extrauterine malignancy (9). To the best of our knowledge, our series of eight patients diagnosed from a Pap smear is one of the largest and demonstrates that Pap smears can also be effective in the early detection of such tumors. Half of the patients in this series were totally asymptomatic and the other half had non-specific symptoms of abnormal bleeding.

DISCUSSION

Malignant cells seen on Pap smears from extrauterine cancers can come from direct extension to the cervix or vagina, as a result of vascular metastasis or as exfoliated cells shed down the fallopian tubes (4,11). The presence of extrauterine cancer

cells in Pap smears also depends upon the site, presence of ascites and patency of fallopian tubes (12). Given the small dimensions of the cervix, the high content of fibrous tissue and lymphatics draining away makes the cervix unfavourable to metastasis but abnormal Pap smears may indicate an advanced disease in a patient with known extrauterine cancer (13). Of the eight patients in the current series, seven had no direct extension to the cervix of cervical metastasis, making passage though the fallopian tubes seemingly the most common mechanism. There were also no ascites detected in any of these patients.

The most common primary sites of extrauterine cancer are ovary, gastrointestinal tract, fallopian tube and breast. Extracervical malignancies on Pap smears are usually of a glandular nature and are rarely squamous carcinomas, sarcomas or lymphomas (14,15) The metastasis may be recognized by unique cytological features or because of the unusual presence of atypical cells different from the normal cervicovaginal cell pattern. The majority of metastatic tumors are characterized by a clean background or absence of tumor diathesis (1) The patient with transitional cell carcinoma in the current series had a clean background. Serous and clear cell carcinoma cells shed single cells, whereas endometrioid carcinoma cells shed cell groups and papillary structures (12). Patient no 2 in the current series had papillary structure and cell groups, and Patient no 3 had dispersed single tumor cells.

In the scenario of very limited atypical cells, molecular technologies may aid the diagnosis. Kinde et al. demonstrated that massively parallel sequencing of somatic mutations in DNA shed from ovarian cancers could be detected in standard liquid-based Pap test specimens (6). Arildsen et al. also detected a mutation in an archival sample of Pap smear obtained 20 months prior to the ovarian cancer diagnosis (16). Similarly, Wang et al. were able to identify the mutations in routinely collected Pap smears from the cervix in 33% of previously diagnosed ovarian cancer and 81% of previously diagnosed uterine cancer. Combining cervical sampling with a plasma test for circulating tumor DNA has been shown to further increase the ovarian cancer detection rate (17).

CONCLUSION

From the results of this study, it can be speculated that Pap smear, especially in cases of abnormal glandular cytology, may be associated with extrauterine cancer. Rigorous screening and precise morphological analyses with an extensive clinical approach are vital for diagnoses of extragenital malignancies. Large-scale investigations with more subjects and investigation of molecular methods for more extensive detection may enlarge the role of Pap smear in the detection of extrauterine cancers.

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