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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Well-Differentiated Papillary Mesothelioma of the Peritoneum: A Retrospective Study from the RENAPE Observational Registry

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ABSTRACT

Background. Well-differentiated papillary mesothelioma of the peritoneum (WDPMP) is a rare entity. Questions regarding management are still being debated as no more than 50 cases have been reported in the literature.

Objective. We aimed to analyze the clinical, therapeutic, and prognostic data of patients with WDPMP from the RENAPE observational registry.

Patients and Methods. All patients diagnosed with WDPMP and prospectively included in the RENAPE national registry between 2010 and 2018 were also included in our study. Expert pathologists from the RENAPATH group confirmed all cases. All clinical, therapeutic, postoperative, and prognostic data were extracted and analyzed.

Results. We report on 56 patients with a mean age of 52 years (range 21–74). WDPMP was incidentally diagnosed during imaging or surgery in 16% and 36% of patients, respectively, and an association with synchronous malignancy was found in 18% of patients. Nine lesions showed discrete signs of fatty invasion. The median Peritoneal Cancer Index was 11 (range 0–33). Eleven patients were treated with definitive excision, 4 were treated with cytoreductive surgery (CRS) only, 37 were treated with CRS and hyperthermic intraperitoneal chemotherapy (HIPEC), and 2 were treated with CRS plus HIPEC plus early postoperative intraperitoneal chemotherapy. CRS was considered to be complete in 90% of cases. One patient died postoperatively and 16 patients (31%) faced postoperative complications. The median disease-free survival was 144 months; Four patients relapsed, with a median period of 27 months. No prognostic factors could be identified.

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Conclusions. Our analysis confirms the favorable prognosis of WDPMP. CRS and HIPEC could be a therapeutic option for diffuse, symptomatic, and/or recurrent disease.

Primary mesothelioma of the peritoneum is a rare disease with an annual incidence rate of two cases per million.[1] Prognosis is generally poor due to the diffuse invasion of the peritoneal surface, with a median overall survival close to 1 year.[2] Diffuse malignant peritoneal mesothelioma (DMPM) are best managed with a combination of surgical cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC).[3] Well-differentiated papillary mesothelioma of the peritoneum (WDPMP) is an exceptional histological subtype of peritoneal surface malignancy. Using the term "well-differentiated papillary mesothelioma peritoneum NOT pleural", we searched the Pubmed electronic database and retrieved 50 articles (single case reports, small series, or relatively larger reviews of pathological consultation files with incomplete follow-up). WDPMP is usually incidentally discovered during treatment of other conditions and is mostly a benign tumor. However, on occasion it is possible that the tumor may behave like a low-grade cancer, or even transform into an authentic DMPM.[4,5]

The typical pathologic features of WDPMP include well-defined papillary structures with fibroconnective tissue cores lined by a single layer of epithelioid mesothelial cells that spread superficially, with absence of mitotic activity and no invasion. Immunohistochemistry can help to identify mesothelioma cells, discriminate a aggressive malignant disease, and quantify the proliferation rate.[6,7] It has recently been identified that somatic missense mutations in either the TRAF7 or CDC42 genes drive the molecular pathogenesis of WDPMP.[8]

No uniform treatment strategy has been established.[9,10] Complete surgical resection has been favored by some authors, and less aggressive surgical approaches by others. Following multimodality treatment, 5-year overall survival (OS) and progression-free survival (PFS) were 90.0% and 79.7%, respectively. Incomplete cytoreduction and poor performance status correlated to both reduced OS and PFS after cytoreduction and HIPEC.[11]

In this study, we report on the series of cases of WDPMP from the RENAPE database. All patients were treated homogenously.[12] We aimed to better understand the natural history, management, and outcome of WDPMP, and to investigate potential prognostic factors.

MATERIALS AND METHODS

The RENAPE Observational Registry

As part of the 2009–2013 Cancer Plan, RENAPE, the national network for the treatment of rare primary peritoneal surface malignancies (PSMs), was set up in 2009 to harmonize the management of these malignancies.[13]

Since 2010, all new patients diagnosed with primary PSMs have been enrolled in the RENAPE registry (ClinicalTrials.gov identifier: NCT02834169), a partner of the European Platform for Rare Disease Registries (EPIRARE). Along with epidemiological, clinical, therapeutic, and follow-up standardized data, local pathologists validated and recorded the histological subtype at each participating site; a group of expert pathologists (RENA-PATH Group) supports this network.[12] Data quality was assured by pretesting and consistency checks during data entry, when applicable.

Patients

We extracted all confirmed cases of WDPMP from the RENAPE registry as of August 2017, and all samples were reviewed by the RENA-PATH Group.[14]

Treatment

Therapeutic indications were validated during multidisciplinary meetings held at expert centers within the RENAPE network.

The standard surgical approach involves peritonectomy and visceral resection, i.e. cytoreductive surgery (CRS).[15–18] Peritonectomy was performed with the intent of removing macroscopic nodules, together with involved peritoneum.[18] The volume and extent of tumor were assessed using the Peritoneal Cancer Index (PCI) determined intraoperatively. A score of 0–3 was recorded for each of 13 abdominopelvic regions, which generates a maximum PCI of 39.[19] Residual disease after CRS was assessed using the complete cytoreduction (CC) score.[20]

The main chemotherapy regimens used intraperitoneally in PSM included cisplatin with mitomycin C or doxorubicin, and oxaliplatin alone or combined with irinotecan.[21,22] When applicable, early postoperative intraperitoneal chemotherapy (EPIC) was performed during the first 5 postoperative days, with either mitomycin C or paclitaxel.[23]

Outcome

Postoperative complications were evaluated within 90 days after surgery and were graded based on the

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Major complications of grades 3 (severe), 4 (life-threatening) and 5 (fatal) were analyzed.[24]

The postoperative follow-up of all patients with PSMs reported in the RENAPE registry included physical examination and thoracic/abdominal computed tomography (CT) scan every 3 months during the first 2 years, then every 6 months for 3 years, and annually thereafter. Recurrent disease or progression was confirmed pathologically.

Statistical Analysis

An intention-to-treat analysis was performed, and postoperative deaths were included in the OS analysis. OS and PFS, determined from the time of diagnosis to death or progression, respectively, were used as the primary endpoints. Survival curves were created using the Kaplan–Meier method and were compared using the log-rank test.

Univariate and multivariate Cox proportional hazards models were adjusted. For multivariate analysis, a stepwise selection of covariates with entering and removing limits of $p < 0.20$ and $p > 0.05$, respectively, was used. Qualitative variables were only included in the models if they had a frequency of each factor level ≥ 0.33, and quantitative variables were only included if they had less than 50% missing values, in order to limit artefacts. All statistical analyses were performed using R version 3.5.1.[25] A significant difference was defined as a p value < 0.05.

RESULTS

Population Characteristics

Among 2520 patients registered in the RENAPE database between October 2010 and August 2017, 56 presented with WDPMP. The median age at diagnosis was 52 years (range 21–74), and the sex ratio was 0.27. Three patients were known to have previously been exposed to asbestos (Table 1).

WDPMP was initially discovered as follows: imaging (16%), abdominal/pelvic pain (29%), increase in abdominal perimeter/ascites (7%), or incidentally during a scheduled abdominopelvic surgery (36%), particularly for herniation (7%) or cancer (7%). In the remaining patients, the disease was discovered under other circumstances, i.e. sterility work-up, gastrointestinal bleeding, or bowel obstruction.

In all patients, the performance status at diagnosis was ≤ 1. In 10 patients (18%), WDPMP was incidentally found during a surgical procedure for a synchronous malignancy. Eight patients were diagnosed with gastrointestinal malignancies, i.e. gastric ($n = 2$) or colic adenocarcinoma ($n = 6$), including one patient with synchronous multiple liver metastases. In addition, one patient with bilateral breast carcinoma associated with BRCA1 germline mutation was diagnosed during prophylactic adnexectomy, and one patient was initially operated on for a retroperitoneal liposarcoma.

Diagnostic Characteristics

Initial work-up included the following preoperative examinations: thoraco-abdominopelvic CT scans in 69% of patients, abdominal magnetic resonance imaging in 29% of patients, and [18F]fluoro-2-deoxy-D-glucose positron emission tomography (^{18}FDG-PET) in 17% of patients. Among the 11 patients explored, none showed elevation of carcinoembryonic antigen (CEA), cancer antigen (CA) 125 or CA19.9 blood tumor markers.

For 76% of patients, diagnosis was made during a surgical procedure (laparoscopy for 63% of patients). Eleven patients required multiple interventions for diagnostic purposes, mainly laparoscopies. Grossly, single or multiple gray white nodule(s) or mass(es) were noted on mesothelial surfaces. The disease was multifocal in 34 patients and localized to the following peritoneal sites in the remaining patients: greater omentum (six patients), lesser omentum (two patients), pelvic spaces (five patients), perihepatic (one patient), anterior parietal peritoneum (one patient), and pre-gastric visceral peritoneum (one patient). For two patients, the disease was unifocal without further details.

A synchronous CRS was performed during diagnostic surgery in 23% of the operated patients, but was deemed incomplete for two of these patients.

Pathology

Fifty-six patients were considered to have WDPMP after central review; no cell atypia was reported in this study, and nine lesions (22%) showed discrete signs of fatty invasion. A multicystic differentiation was noted for four lesions. Ascitic fluid analysis was positive in seven patients who presented with multifocal disease.

Treatment Characteristics

Eleven patients were treated by definitive excisional biopsy. Ten patients received neoadjuvant chemotherapy prior to CRS, with a median of six cycles.[1–12] Among these patients, five received an adapted regimen for a previously diagnosed advanced gastric ($n = 2$), colorectal ($n = 2$), or bilateral breast cancer ($n = 1$). The other five patients

TABLE 1 Population, treatment, and outcome characteristics

	Data available	Total [n = 56]	Multifocal disease [n = 34]	Unifocal disease [n = 18]	Unspecified [n = 4]
Median age, years (range)	56	52 (21–74)	44 (27–74)	59 (21–72)	62 (46–66)
Sex ratio	52	0.27	0.21	0.33	0.33
Presentation					
Imaging findings	55	9 (16%)	5	2	2
Pain		16 (29%)	14	2	0
Incidentally during surgery		20 (36%)	12	8	0
Ascites		4 (7%)	1	3	0
Other		6 (11%)	2	3	1
Synchronous cancer diagnosis or management	56	10 (18%)	5	4	1
Positive diagnosis	45				
No invasive procedure		11 (24%)	8	3	0
Invasive procedure [n = 34]	34				
1 diagnostic laparoscopy		22 (65%)	18	2	2
1 diagnostic laparotomy		14 (41%)	8	5	1
Multiple diagnostic procedures		11 (32%)	7	3	1
Synchronous CRS		8 (24%)	4	4	0
Pathology					
Invasion	41	9 (22%)	7	2	0
Positive ascitic fluid analysis	16	7 (44%)	7	0	0
Treatment					
Neoadjuvant CT	54	10 (18%)	7	2	1
Local treatment [n = 54]	54				
Excisional biopsy		11 (20%)	1	10	0
Definitive CRS		4 (7%)	3	1	0
CRS-HIPEC		37 (69%)	28	6	3
CRS-HIPEC-EPIC		2 (4%)	2	0	0
Adjuvant CT		5 (9%)	4	0	1
Operative findings					
Median PCI (range)	27	11 (0–31)	11 (4–25)	4.5 (0–31)	11 (5–13)
CCR0 score	39	35 (90%)	26	6	3
CCR1 score		4 (10%)	4	0	0
Early complications					
Grade 4 medical complications	52	8 (15%)	6	1	1
Grade 2–3 medical complications		10 (19%)	9	1	0
Additional surgery		8 (15%)	5	1	2
Late complications					
Additional surgery	38	3 (8%)	2	1	0
Outcome					
Local relapse	38	4	4	0	0
Median delay, months (range)		27 (20–123)	27 (20–123)	NA	NA
Distant relapse		0	0	0	0

Percentages were calculated using patients for whom relevant information was available

CT chemotherapy, *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *EPIC* early postoperative intraperitoneal chemotherapy, *PCI* Peritoneal Cancer Index, *CCR* completeness of cytoreduction, *NA* not applicable

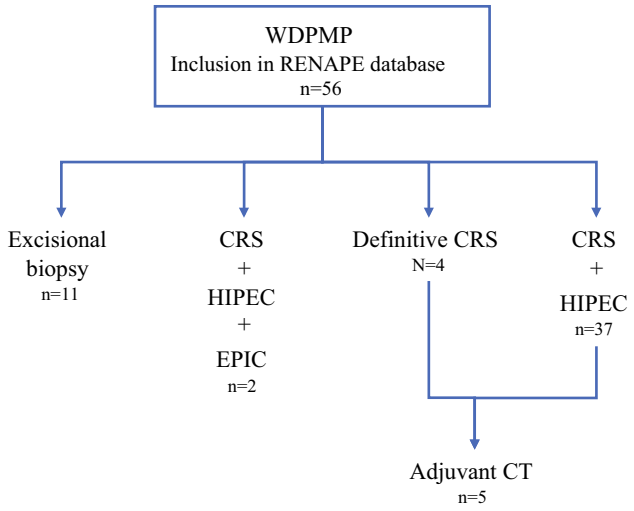


FIG. 1 Study selection process. Therapeutic data are missing for two patients *CT* chemotherapy, *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *EPIC* early postoperative intraperitoneal chemotherapy, *WDPMP* well-differentiated papillary mesothelioma of the peritoneum

received a platinum-based chemotherapy with a taxane or a folic acid analog for a multifocal WDPMP.

Forty-three patients underwent CRS, none via the laparoscopic route: 37 patients underwent CRS combined with HIPEC, two underwent CRS associated with HIPEC and EPIC, and four underwent definitive CRS. The median duration of surgery was 330 min (range 180–480), the median PCI was 11.0 (range 0–31), and the CC score was optimal: 0 or 1 in 90% and 10% of patients, respectively. In nine patients, a splenectomy was performed alongside CRS.

HIPEC was delivered to 39 patients, with an open abdomen in 87% of patients, and a median duration of 60 min (range 30–120) depending on the drug used intraperitoneally. The median temperature was 42.4 °C (range 38–44). The following regimens were used (intraperitoneal dose, in order of decreasing frequency): cisplatin 50 mg/m^2 + liposomal doxorubicin 15 mg/m^2, oxaliplatin 360 mg/m^2 + irinotecan 240 mg/m^2, oxaliplatin 360 mg/m^2 alone, cisplatin 75 mg/m^2 alone, cisplatin 50 mg/m^2 + mitomycin C 35 mg/m^2, mitomycin C 35 mg/m^2 alone and cisplatin 50 mg/m^2 + doxorubicin 20 mg/m^2.

Two patients underwent adjuvant EPIC with paclitaxel or docetaxel (20 mg/m^2), administered during the first 5 postoperative days, and five patients with advanced disease and/or synchronous malignancy underwent adjuvant chemotherapy initiated within 2 months of CRS. Different regimens were delivered, notably cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2. LV5FU2 (folinic acid, 5FU bolus, then 5FU infusion on D1 and D2) was delivered in one patient (colic cancer) and oxaliplatin + epirubicin was delivered in another two patients (gastric cancer). None of the patients received adjuvant radiation therapy (Fig. 1).

Outcome

Postoperative Period The median length of stay in the intensive care unit was 4.5 days (range 0–71), for an overall stay of 15 days (range 8–91). Forty-one postoperative complications (any grade) were reported in 16 patients (31%), and all were treated with CRS and HIPEC.

Eight patients experienced life-threatening medical complications, i.e. acute respiratory distress syndrome, septic thrombophlebitis, acute renal failure requiring dialysis, bilateral acute pyelonephritis, sepsis as a complication of peritonitis, venous then arterial gas embolism complicated with heart failure, and arrhythmia. One patient died of multivisceral failure 12 days after surgery.

Eight patients experienced surgical complications requiring an additional laparotomy: one for evisceration, two for evisceration associated with hemoperitoneum, one for ileocolic fistula, peritonitis and hemoperitoneum, two for isolated hemoperitoneum, one for occlusion requiring colostomy, and one for peritonitis. Most of these patients also experienced grade 2–3 medical complications such as thrombocytopenia (n = 2; one required a transfusion), anemia (n = 1), inflammatory fever (n = 1), arrhythmia (n = 2), anorexia (n = 3), diarrhea (n = 2), melena (n = 1), pleural effusion (n = 3), and renal failure (n = 3).

Longer-Term Follow-Up and Oncological Results The median follow-up for the 38 documented patients, after initial diagnosis, was 52 months (range 3–211). Three patients were reoperated after a median interval of 40.5 months (range 4.5–129) after CRS: one for an enterocutaneous fistula, one for occlusion requiring a right transverse colostomy, and the last patient was repeatedly reoperated for resection of a desmoid tumor, drainage of peritonitis, axillo-femoral bypass surgery to treat septic thrombosis, and closure of ileostomy, in chronological order. Four patients required medically assisted procreation, with success.

The median relapse-free survival was 144 months; however, a confidence interval could not be calculated due to the large amount of censored data.

One patient died during the initial postoperative period, and four patients, all with initial multifocal disease, relapsed on the peritoneal surface after a median period of 27 months after the first CRS (range 20–123). One patient received a second CRS followed by HIPEC with cisplatin + liposomal doxorubicin, without complications, 28 months after the first CRS + HIPEC (the second with a

closed abdomen). Another patient received two additional lines of chemotherapy with cisplatin + pemetrexed, then bevacizumab, 123 months after the initial CRS associated with HIPEC and EPIC. The patient initially presented with ascites and the following postoperative characteristics: PCI 12 and CCR1. A third patient initially managed with CRS + HIPEC was biopsied for two pathological granulations of 1 and 2 mm, with no evidence of invasion, and was then watched. The last patient underwent bilateral adnexectomy with CRS and a second HIPEC (cis-platin (CDDP) + doxorubicin) 30 months after the first definitive CRS. The patient initially presented with microinvasive foci. None of these patients received systemic chemotherapy at any point in their course. As of the latest update, all were still alive without evidence of tumor recurrence.

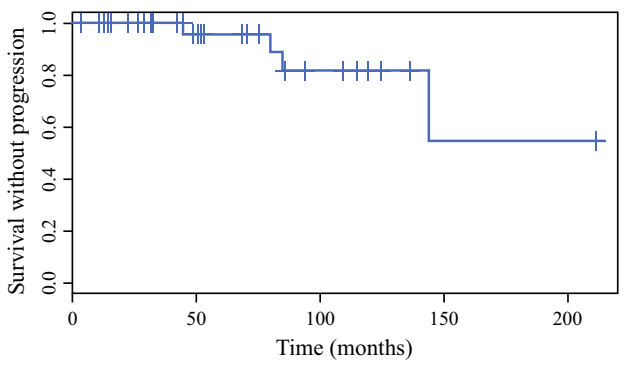
Prognostic Factors of Progression-Free Survival

We performed a prognostic survival analysis of 55 patients, 19 of whom were censored. No variable reached the significance threshold, either in univariate or multivariate analysis. This result may be attributed to the small sample size and number of events (Fig. 2).

DISCUSSION

Registries of rare cancer patients represent a fundamental research tool by pooling data from fundamental, clinical, and epidemiological research. More than 2000 patients with PSMs were registered in the French RENAPE registry as of 2017.

With the inclusion of 56 patients in our study, it is the largest cohort reported to date and includes a central pathological review of all confirmed WDPMP cases. The



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time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
44.6	22	1	0.955	0.0444	0.871	1
80.3	14	1	0.886	0.0776	0.747	1
85.2	13	1	0.818	0.0970	0.648	1
144.0	3	1	0.545	0.2319	0.237	1

FIG. 2 Local relapse-free survival. *CI* confidence interval, *std.err* standard error

differential diagnosis with other PSMs may be complicated, especially when the sample size is small and rare mesothelial cells are observed in the axes of the papillae.[6] One of the patients in our series was requalified. Ascitic fluid cytology is often inconclusive, especially in distinguishing between malignant and benign mesothelial proliferations.[26] CT-guided core needle biopsy or laparoscopic biopsy may provide sufficient material to establish a diagnosis using histology and immunohistochemistry, which usually requires a panel of antibodies. For all these reasons, we recommend anticipated diagnostic and therapeutic management in expert centers.

Three patients had a history of previous asbestos exposure, and, although uncommon, this association has been previously reported twice.[27,28]

It seems of paramount importance to diagnose WDPMP with a sufficient degree of probability as overtreatment can be highly toxic, as evidenced in our series. WDPMP is generally considered a low-grade malignancy, with a high survival rate following complete surgical resection. We observed a relapse-free survival rate that is comparable (or even better) with the largest published cohorts ($n \geq 20$), even though we managed our patients more aggressively.[5,29,30] All patients in our series who relapsed on peritoneal surface initially presented with multifocal disease and adverse pathologic indicators (CCR $\geq$ 1, elevated PCI, invasive foci, or ascites). Unlike a recent study, preoperative CT was uncommon in our series and adjuvant systemic chemotherapy does not seem to bring added value.[29] As advocated by Malpica et al. and Churg et al.[6,30] we considered particular WDPMP with invasive foci in the papillae to be prone to multifocality and recurrence. Such entities could be treated more aggressively, even if our study lacks the power to identify a prognostic correlation between papillae invasion and PFS. It should be noted that one patient in our series benefited from two extensive surgeries, both followed by HIPEC with no major toxicity. As previously reported, WDPMP is also able to evolve in truly malignant mesothelioma,[31] which also explains why the disease is aggressively treated in some centers with CRS + HIPEC, and eventually EPIC.

On the other hand, none of the patients treated with definitive excisional biopsy relapsed in our series. Such patients (except one) presented with unifocal disease and indolent pathologic features. Accordingly, in previously published series, the patients with single lesions were usually asymptomatic, and none experienced recurrence following tumor excision.[6,9] For these patients, CRS/HIPEC may be seen as overtreatment for low malignant potential, and complete excisional biopsy in completely resectable localized lesion(s) could be recommended. If complete resection is unavailable for asymptomatic patients, close follow-up could be an appropriate option.[9]

Our series is likely not large enough, with too few events, to identify prognostic factors and stratify the magnitude of the treatment. Interestingly, median PFS tends to be better in patients with multifocal disease compared with those with unifocal disease, which may be attributed to therapeutic aggressiveness in multifocal disease.

Strikingly, WDPMP and colorectal cancer were discovered simultaneously in five patients, as previously reported.[32–36] For all five patients, the levels of digestive tumor markers were normal at diagnosis and microsatellite instability status was not available. None of these patients relapsed as a result of WDMPM. Gynecological malignancies have also been reported to be associated with WDPMP, but not in our series.[6,28,37,38] The molecular events initiating or driving the oncogenesis of WDPMP are not known, but a common molecular basis appears improbable when considering the high prevalence of colorectal or gynecological cancer.

CONCLUSIONS

In this observational registry of patients with WDPMP, we have collated important clinical and prognostic data for this rare disease. The treatment of WDPMP is controversial, and it seems essential to manage this very rare entity within national clinical and pathological networks. We would recommend definitive complete excisional biopsy in completely resectable localized WDDPM, and CRS/HIPEC for selected patients with multifocal WDPPM, or disease with invasive foci in the papillae.

DECLARATIONS

The RENAPE observational registry was approved by the Advisory Committee for Data Processing in Health Research at the French Ministry of Research (CCTIRS; no. 10.257) and the French Data Protection Authority (CNIL; no. DR-2010-297), and complies with the ethical principles laid down in the Declaration of Helsinki. The registry has been implemented through a fully web-based application (EOL©),[13] and data hosting is secure and safe based on Information Technology Infrastructure Library security management (version 3).

This study was approved by the RENAPE Scientific Committee and the Ethics Committee for the Protection of Individuals in Clinical Research prior to data extraction.[10]

The RENAPE scientific committee accepts direct responsibility for this manuscript.

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