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Well-Differentiated Papillary Mesothelioma Complete Response after Laparoscopic Hyperthermic Intraperitoneal Chemotherapy (LHIPEC) Plus Intraperitoneal Chemotherapy; And a Review of the Literature

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Abstract

Well-Differentiated Papillary Mesothelioma (WDPM) is a relatively rare disease with an indolent nature. However, due to its rarity, treatment policies differ between hospitals. The presented case was diagnosed with well-differentiated papillary mesothelioma after a diagnostic laparoscopy. She was treated with laparoscopic hyperthermic intraperitoneal chemotherapy followed by intraperitoneal chemotherapy and oral S-1 treatment. After three months, the patient underwent surgery with curative intent, with removal of all suspicious peritoneal sectors. Pathologic findings showed no residual tumour and normal mesothelial cells.

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Introduction

Well-differentiated papillary mesothelioma (WDPM) is formally classified as a small subgroup of mesothelioma with benign behavior, subsequently renamed "well-differentiated papillary mesothelial tumor" (WDPMT) in the 2021 WHO classification [1]. Although most cases follow a benign course, some cases progress to malignant transformation [2]. Regarding treatment, there is no consensus about this relatively rare disease. Here, we report a case treated with Laparoscopic Hyperthermic Intraperitoneal Chemotherapy (LHIPEC) and post-operative intraperitoneal chemotherapy with a complete pathologic response confirmed by definitive surgery.

Case Presentation

A 55-year-old woman with a history of diabetes and hypertension had lower abdominal pain since September 2022. She underwent laparoscopic examination that showed several peritoneal tumors (Figure 1,2). Pathologic examination confirmed the presence of well-differentiated papillary mesothelioma (Figure 3,4). She was transferred to our institution for further treatment. Imaging showed peritoneal thickening and ascites. Repeat laparoscopy in March 2023 showed several whitish nodules 2–5 mm in diameter on the peritoneal surface, with a total PCI (peritoneal cancer index) of 16. (Figure 1,2). We performed omental tumor biopsy and delivered LHIPEC with gemcitabine 1g + cisplatinum 50 mg at 43 degrees Celsius for 60 mins. After surgery, the patient was treated with intraperitoneal chemotherapy (docetaxel, cisplatin) combined with oral S-1 combination chemotherapy. Her final operation in June 2023 showed a markedly reduced peritoneal tumor load, with the PCI decreased to 3 and residual nodular lesions in the omentum and pelvis. We performed a combined pelvic and bilateral paracolic-gutter peritonectomy, total abdominal hysterectomy with a bilateral salpingo-oophorectomy, and low anterior resection to achieve complete resection. The final pathologic report showed no residual tumor and a normal, flat mesothelial cell lining (Figure 5). She was discharged uneventfully on postoperative day 16.

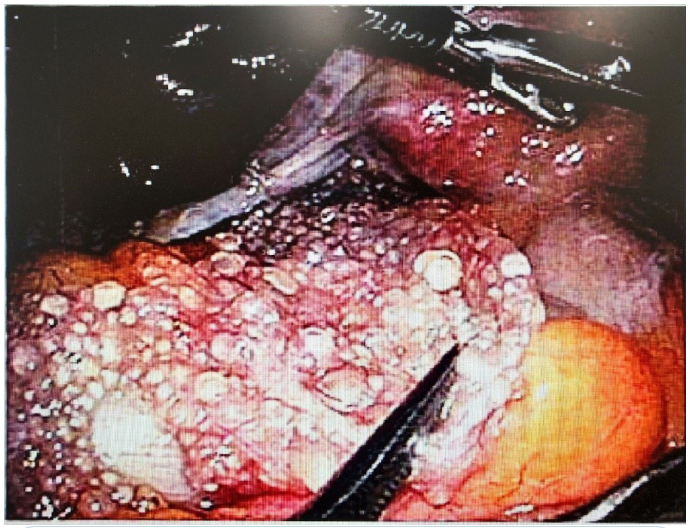

Figure 1: Laparoscopic examination showed multiple whitish tumors involving the omentum.

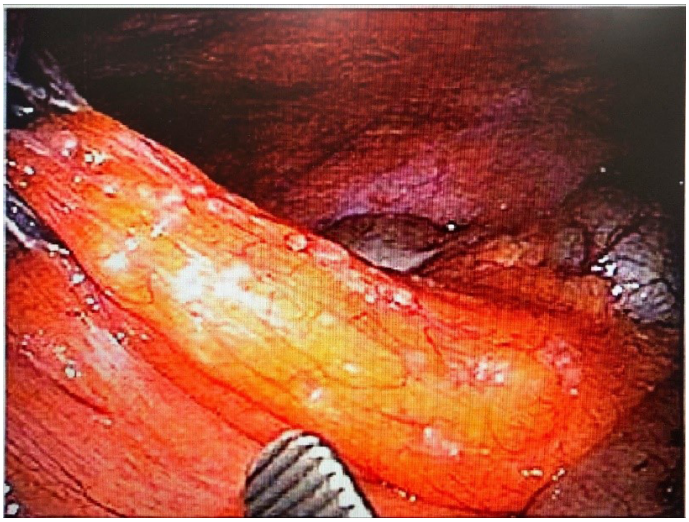

Figure 2: Laparoscopic view of the omentum with multiple whitish tumors, 2~5mm in size.

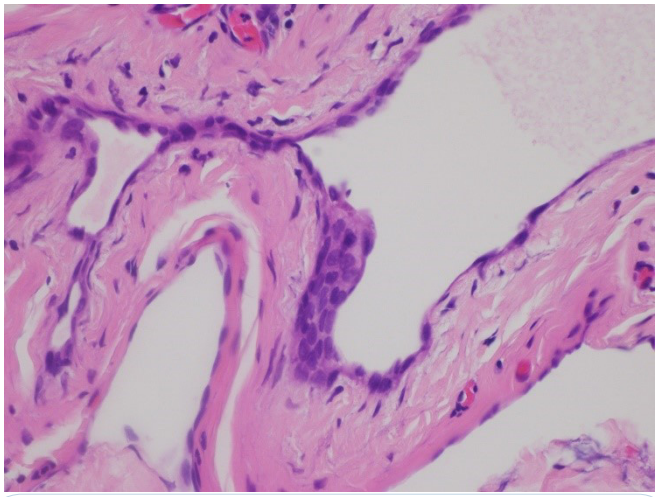

Figure 3: Pathologic examination showed a cuboid mesothelial lining (H&E stain) centrally, compared with normal mesothelial cells on the right.

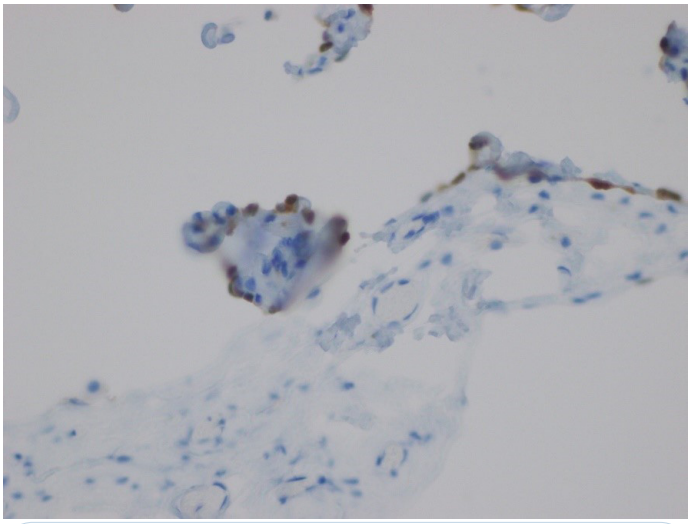

Figure 4: Tumor cells stained positive for BAP1.

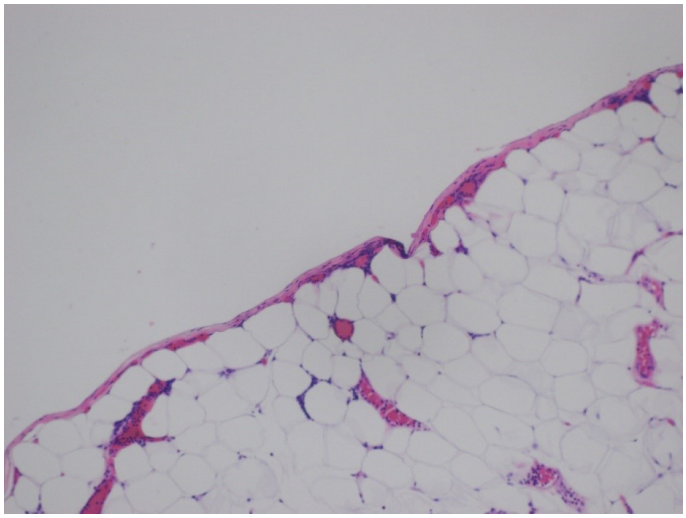

Figure 5: After treatment, the histology from the 2nd operation showed a lining of normal mesothelial cells.

Discussion

In 1981, Foyle A et al. reported the first 25 female cases of this peritoneal tumor. Eight cases had WDPM with indolent behavior [3]. Subsequently there have been scattered cases reports with varying treatment policies (Table 1). A total of 306 cases were identified with an average age at diagnosis of 48 years. There is female predominance with a male/female ratio of 71/231 (four cases unknown). Most tumors were found incidentally during surgery for another reason, but other symptoms included pain and ascites causing abdominal distension. Before 1990, patients may have been treated with radiotherapy after surgery. However, after Daya reported two cases of postoperative radiation therapy with concerning complications (one died two years later from radiation enteritis; one died within 6 weeks of surgery and radiotherapy), radiotherapy has no longer been used for this disease. In their report, the authors suggested adjuvant therapy be used only when there is clear evidence of progression [6]. Most cases were treated with surgery alone (complete or incomplete resection) with acceptable complications and outcomes. Malignant transformation has however been reported. Among the 306 cases, five were reported to undergo malignant transformation at intervals of 1.2.2.7 and 15 years. [5-39] All cases were diffusely distributed initially and three underwent biopsy alone (with non-curative intent) at initial surgery. (Regarding the other two cases one with multiple lesions on the omentum underwent omentectomy and for the other, details are not mentioned). Due to the relative benign nature of the condition, it was thought reasonable to simply remove diagnostic tissue instead of resecting all visible lesions. However, WDPMT had been found to co-exist with other malignancies [40-45,50,51]. In addition, after the WHO redefined the diagnosis,we realized that there are two groups of disease that mimic one another under the microscope: true WDPMT and mesothelioma in situ. Accurate diagnosis of WDPMT requires examination of the entire lesion to exclude the possibility of superficial sampling from a component of an invasive diffuse mesothelioma [1]. In the 2019 study by Deraco, they reported that differentiation between DMPM and WDPPM may be challenging when based solely on morphological criteria. Thus cases with aggressive biology may actually represent cases of DMPM and cases with DMPM may be initially diagnosed as WDPPM and undertreated, when excisional biopsy or observation are used. They recommended further confirmation using molecular targets such as BAP1 and checks for mutations in TRAF7 and CDC42.[40] In a 2022 review, Churg et al [52]. also suggested routine checks that use immunostaining for BAP1, and if necessary MTAP or CDKN2A FISH on WDPMT. Several recent studies focus on genetic differences that might distinguish WDPM from malignant mesothelioma [53,54]. Because the prognosis of WDPM is very different form that of malignant mesothelioma, further treatment based on such genetic studies may be very valuable.

In the field of WDPMT treated by cytoreductive surgery with HIPEC, two large institutes (PSOGI and RENAPE) reported their results in 2019 [40,41]. The post-operative mortality was 2 of 111 cases. The post-operative major complication rate is around 20% (PSOGI: 24% and RENAPE reported grade 4 complications in 15%). Regarding recurrent cases, PSOGI had 8/45 recurrences (all within 5 years) and RENAPE had 4/56. In these two reports, the authors do not mention whether pathological findings after recurrence still showed WDPMT or malignant transformation to mesothelioma. The relatively high recurrence rate might be associated with selection bias due to more severe cases (median PCI 9 and 11 in each group) being referred to receive this type of surgery.

In 2013, Lee et al reported two cases with disseminated WDPM treated with systemic chemotherapy (5-FU/CDDP x12cycles and Pemetrexed/CDDP x 8 cycles), with complete responses. These two cases had no evidence of disease after 96 and 18 months, respectively [33]. In 2017, Bazine also reports a case of disseminated WDPM treated with systemic chemotherapy (Pemetrexed/CDDP x 6 cycles) with a complete response. This patient had NED for 9 months [37]. In all three cases, a complete response was determined based on imaging and clinical findings only. Our patient had complete surgical removal of residual suspicious sites, confirming a complete response on pathological examination.

In 2010, Clarke et al reported a case with WDPM that had long-term follow-up for 24 years. This is the longest reported survival. However, she had three recurrences and underwent repeated surgeries. She also received adjuvant intraperitoneal and intravenous treatment and her course was complicated by anthracycline-induced heart failure, eventually managed with heart transplantation. She remains alive but after 24 years is not free of disease [25]. Acknowledging the concept proposed in 1990 [6], adjuvant treatment should be reserved for cases with evidence of progression. In 2013, Lee proposed the following therapeutic strategy: 1) for resectable disease, perform complete resection to minimize the risk of underdiagnosis; 2) for an irresectable condition, the patient who is asymptomatic with localized tumor extent can simply be followed up closely; 3) an irresectable condition with extensive disease or symptoms can be treated with chemotherapy. Here we suggest that local treatment using LHIPEC together with intraperitoneal chemotherapy and oral S-1 treatment might be a safe and effective treatment with a demonstrable pathologic response. Since WDPM comprises a thin lining of mesothelial cells, it is reasonable to treat the peritoneal surface. Applying a chemotherapeutic agent to the peritoneal surface allows easier penetration than occurs with a traditional intravenous route [55]. Although most chemotherapeutic drugs act on a specific part of the cell cycle, with the aid of heat above 43 Celsius, most cancer cells will be destroyed [56]. Combining the two mechanisms, hyperthermic intraperitoneal chemotherapy is advantageous in treating such diseases.

Table 1: Clinical characteristic & treatment with outcome.

First author	Year	Age (median)	M/F	No. of patient	Symptom	Site/Severity	Treatment	Outcome
Raju [4]	1989	24	0/2	2	Mass 2	multiple, localized	tumor excision + radiotherapy	NED for 11 yrs & 20 yrs
Burrig [5]	1990	52	2/0	2	Incidental 2	both multiple, diffuse	biopsy only	one pt with malignant mesothelioma transformation after two yrs
Daya [6]	1990	40	4/18	22	Incidental 6; Pain 5; Mass 3; Ascites 3; Others 5	mainly omentum, pelvis, ovary	Nil: 11 Operation:8 C/T:4 R/T:5	two patients received R/T and died (one radiation enteritis; one within 6 weeks of surgery) ; in no treatment group 8/11NED for 1~14yrs
Lovell [7]	1990	11	0/1	1	Pain 1	diffuse	C/T+ surgery+GnRH agonist	AWD > 9 months
Mangal [8]	1995	35	0/1	1	Pain 1	omentum, pelvis,	excision only	NED for 1 yr
Hoekman [9]	1996	36	0/3	3	Incidental 3	omentum, pelvis, diaphragm	tumor excision only	all NED for 7/6/1 yrs
Shukunami [10]	2000	56	0/1	1	Incidental 1	Diffused (omentum, pelvis)	tumor excision, IV/IP/Ip carboplatin	C/T effective to reduce ascites and pleural effusion; NED for 4 yr
Kim [11]	2001	60	0/1	1	Ascites 1	omentum	excision only	malignant mesothelioma at trocar site, ascites at 2 year interval
Butnor [12]	2001	44	5/1	6	Pain 3; Ascites 2	NR	chemo:3, Nil:1, unknown:2	1NED for 3yrs; 1 DOD 3yrs; 2AWD for 5/15 yrs
Porpora [13]	2002	46	0/1	1	Incidental 1	right uterosacral ligament	tumor excision only	NED for 3 yrs
Assaf N [14]	2002	55	1/0	1	Ascites 1	multiple	debulking surgery	NED for 2 yrs
Haba [15]	2003	48	0/1	1	Incidental 1	pelvis only	tumor excision	NR
Meister [16]	2003	45	1/0	1	Ascites 1	parietal peritoneum, omentum	tumor biopsy only	NR
Hoekstra [17]	2005	74	0/1	1	Incidental 1	multifocal	biopsy only	NED 12 mo
Gong [18]	2005	64	0/1	1	Incidental 1	liver surface, single	tumor excision only	NR
Lanneau [19]	2005	21	0/1	1	Incidental 1	posterior uterine fundus, single	tumor excision only	NR
Baratti [20]	2007	34.5	0/8	8	Incidental 4; Pain 2; Infertility 2	PCI:4~23	CRS+HIPEC	7 NED for 6~66 mo, 1DOD 13 mo (coexisting with biphasic mesothelioma)
Guo [21]	2007	41	0/1	1	Pain 1	diffused	biopsy only	alive> 18 mo
Ikeda [22]	2008	73	0/1	1	Incidental 1	diffused	biopsy, C/T with paclitaxel	alive> 11 mo
Collin [23]	2009	46	0/1	1	Incidental 1	NR	surgery only	NED > 9 mo
Wheeler [24]	2009	63	1/0	1	Incidental 1	anterior abdominal wall localized	surgery only	Alive > 13 mo
Clarke [25]	2010	36	0/1	1	Pain 1	diffused	surgery x3, IP and IV C/T	AWD > 24 yrs, C/T related heart failure s/p heart transplant
Hatano [26]	2011	45	1/0	1	Incidental 1	Single, from omentum	tumor excision only	NED for 3 yrs
Malpica [27]	2012	47	0/26	26	Incidental 24; Pain 2	single:13 multiple:13	excision only	22 NED for 5~144mo; one recurrence at 46.5 mo; 3DOC
Nemoto [28]	2012	73	0/1	1	Ascites 1	multiple	S-1--> excision-->C/T TXL+irinotecan/CDDP	progression with maligant transformation 1 year, DOD at 54 mo
Anirudhan [29]	2012	48	1/0	1	Incidental 1	single from hernia sac	tumor excision only	NR
Chen [30]*	2013*	37	4/14	18	Most incidental	single: 8 multiple:10	tumor excision	8 NED for 5~102mo; 7 NETP for 17~136mo; I DOD (coexisting cervical cancer)
Ribeiro [31]	2013	56 & 44	0/2	2	Pain 1	multiple:2	tumor biopsy+ C/T CDDP+pemetrexed :1; C/T CDDP+pemetrexed :1	NETP:1, DOD:1 at 12 yrs
Washimi [32]	2013	58	0/1	1	Incidental 1	multiple	tumor excision only	malignant transformation to mesothelioma at 7 yrs
Lee [33]	2013	53	6/9	15	Incidental 11; Pain 2; Ascites 2	single:8; multiple:7 (localized 3 disseminated 4)	single-->4/8 excision only, 4/8 +C/T; Multiple-->2/7 ex only, 5/7 +C/T	single: NED in 6 for 12~146 mo; DOC in 2; multiple: NED in 2 AWD in 4, DOD in 1 (110 mo)
Val-Bernal [34]	2014	66	1/0	1	Incidental 1	NR	excision of hernia sac	NED for 103mo
Nasit [35]	2014	28	0/1	1	Pain 1	diffused	complete resection	recurrence at 9mo ->C/T with CDDP+doxorubicin
Jakobsen [36]	2016	63	1/0	1	Incidental 1	multiple, localized	tumor excision	NR
Bazine [37]	2017	36	1/0	1	Pain 1	diffuse	biopsy then C/T with CDDP+pemetrexed x6	NED for 9mo
Saha [38]	2018	28	0/1	1	Pain 1	single	resection	NED for 9 mo

Sun [39]*	2019*	40	17/58	75	Most incidental (57/63); Pain 4	20/49 single, 29/49 multiple	NR	f/u data only in 46/75 (39 alive, 1trans-formed to malignant mesothelioma, 6 died from other cancers)
Deraco [40]	2019	44	12/33	45	NR	PCI 9 (5~16)	CRS+HIPEC, preop C/T:8, post op C/T:2,	8 recurrent (4DOD, 4 AWD) all < 5yrs
Vogin [41]	2019	52	11/41(4: missed)	56	Incidental 29; Pain 16; Ascites 4	PCI 0~31 median 11	Excision 11, CRS only 4, CRS+HIPEC 37, CRS+HIPEC+EPIC 2, adjuvant C/T 5	post-op mortality:1, G4 complication: 8, recurrence: 4
Kim [42]	2019	64	5/7	12	Incidental 11	Single 9, multiple 3	excision only	0 recurrence
Bousema [43]	2019	25	0/1	1	Pain 1	single	excision	NR
Erem [44]	2020	68	0/1	1	Pain 1	single	excision	NED > 5 mo
McGinnis [45]	2020	62	0/1	1	Pain 1	multiple	complete excision +RT, C/T (for ovarian and endometrial cancer)	NR (coexisting with ovarian and endometrial cancer)
Pang [46]	2021	37	0/1	1	Incidental 1	multiple	excision	NED for 49 mo
Holford [47]	2021	28	0/1	1	Pain 1	single	excision only	NED 6 wk
Serao [48]	2022	65	1/0	1	Pain 1	NR	biopsy only	DOC(cardiovascular)
Jiang [49]	2022	50	0/1	1	Incidental 1	multiple diffuse	debulking surgery+ adjuvent C/T	NED> 7mo

PCI: Peritoneal Cancer Index; C/T: Chemotherapy; SC: Systemic Chemotherapy; IP: Intraperitoneal; Ip: Intrapleural; NR: Non Reported; NED: No Evidence Of Disease; AWD: Alive With Disease; DOD, Dead Of Disease; DOC, Dead Of Other Causes.
* Duplicate cases in these two series, removed on calculating the total number of cases.

Conclusion

Here we reported a case of WDPM treated with LHIPEC and the post-operative combination of intraperitoneal and oral systemic chemotherapy. The patient then underwent definitive surgery with a maximal resection of peritoneum. We were surprised that the final pathologic report showed no residual tumor. This is the first report to describe an excellent response to the combination of LHIPEC and a two-pronged post-operative treatment approach. LHIPEC combined minimal operative risk with further treatment comprising bi-weekly intraperitoneal chemotherapy combined with oral S-1. This is an alternative, simple and safe approach to treating this condition.

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