Radical Cystoprostatectomy in Patients with Behçet's Disease: The Report of Four Cases and Review of The Literature

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INTRODUCTION

Behçet's disease (BD) is a chronic, relapsing, multisystemic inflammatory disease that is characterised by recurrent oral and genital ulceration with skin and ocular lesions. BD affects other areas of the body, including the joints, blood vessels, nervous system and gastrointestinal system[(1)]. A BD diagnosis is based on clinical criteria, such as the criteria proposed by the International Study Group for BD and, more recently, the International Team for the Revision of the International Criteria for BD[(2,3)]. According to the relationship between malignancy and BD, Fırat et al. found no difference in the incidences of malignancies in relation to BD compared to the incidences of malignancies in the normal population of Turkey.[(4)] With regard to the association of BD with bladder cancer, there is only one reported case with a previous history of prolonged cyclophosphamide therapy[(5)]. Therefore, it is very difficult to determine whether or not BD is related to the pathogenesis of bladder cancer. Also, the relationship of genitourinary cancer with BD is not yet known. There are only a few studies that refer to radical surgery in BD patients, and there is only one case report about radical cystoprostatectomy in a BD patient. Therefore, it is still not well known whether or not pelvic surgery in patients with BD is safe. A radical cystoprostatectomy is a routine surgery performed in our clinic. In this paper, we present our experience with four BD patients who underwent a radical cystoprostatectomy with pelvic lymph node dissection.

CASES DESCRIPTION

Four patients with BD who underwent a radical cystoprostatectomy with pelvic lymph node dissection were retrospectively examined. In our clinic, 457 radical cystoprostatectomies with pelvic lymph node dissection were performed between 2000 and 2015. All of the operations were performed by the same two senior surgeons. Following protocol, each patient was held in the intensive care station for one or two days after the operation. The mean time for the occurrence of BD was 14 years (11-18 years). All patients (n = 4) were treated with Colchicine after diagnosis until the time of operation. Additionally, three of the patients took prednisolone for an interval of 2-5 years. None of the patients had a history of cyclophosphamide consumption, which is a known cause of bladder cancer. The mean age of the patients was 51.5 years. The first patient was a female consuming cholchicine intermittently until 4 months before surgery. Clinical manifestations were oral aphthous stomatitis, genital ulcer, erythema nodosum and maculopustular lesions. The second and third patient were males who presented with oral ulcer, genital ulcer, arthritis and erythema nodosum as clinical manifestations of BD. The medical therapy with cholchicine and methylprednisolone was quitted approximately one year before surgery in the second patient and approximately three months before surgery in the third patient. The fourth patient presented with oral ulcer, genital ulcer and skin lesions. Treatment with cholchicine and prednisolone was concluded two months before operation. None of the patients had indication or history for neurological, vascular and/or gastrointestinal manifestation of BD. Three patients had a history of occupational exposure to carcinogens, and two of the patients had a history of tobacco smoking. No comorbidity, especially any affecting the cardiovascular system, or cardiovascular diseases were present in the patients. The ASA score was 2 in all of the patients. None of the patients had a history of prior surgery and other systemic diseases. The routine preoperative evaluation included an abdominal computed tomography (CT). This pre-evaluation was done for all of the patients with invasive bladder cancer in our clinic. CT results revealed no signs of vascular dysfunction or any pathological indication in the vascular system caused by BD. Further evaluation was not necessary. The perioperative and postoperative periods of the TUR-B operations progressed uneventfully. The patients were referred to rheumatologists for rheumatologic approval. All of the patients were assessed for disease activity by evaluation of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and by clinical examination. None of the patients were in the active phase of BD. Intravenous methylprednisolone therapy was started 72 hours before surgery and was continued until the seventh postoperative day, thereafter oral methylprednisolone therapy was started for two weeks. Routine preoperative bowel preparation with a rectal enema was performed on both the night before and the morning of the opera-

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Table 1. Patients' characteristics

No	Age/Gender	BD diagnosis duration	Medication	Duration of Medication in years	Risk factor of cancer	Pathology	Complication
1	57/Female	13	Cholchicine	13	shoe manufacture	PT2G3N0	Ileal ischemia
2	44/Male	11	Cholchicine/Prednisolone	3	silver foundry	PT3G3N3	No
3	53/male	18	Cholchicine/Prednisolone	5	Aluminum production, smoking 36 packs/year	PT2G3N1 CİS +	Common iliac arter
4	52/male	14	Cholchicine/Prednisolone	14	Smoking 39 packs/year	PT3G3N0	Common iliac arter

tion. Patient characteristics are listed in **Table 1**. Additionally, we determined our first 100 patients as the control group of this study and presented mortality rate, vascular and gastrointestinal complications of the control group in **Table 2**. Information about patient characteristics and complications was obtained retrospectively through chart review by medical doctors. The perioperative and postoperative processes of the four patients were as follows:

The first patient was a 57-year-old female with an invasive tumour diagnosed during the patient's initial TUR-B operation (PT2G3). The perioperative period of the first operation was uneventful. The final pathology after a cystectomy was PT2G3N0 (N14/0). Acute ischaemia occurred during preparation of an ileal conduit in this patient. This part of the ileum had to be re-anastomosed, and an ureterocutanostomic diversion had to be performed. Total blood loss was 500 mL. The postoperative period was uneventful, and the patient was discharged after 11 days. The patient was admitted to our clinic because of urinary infection in the third month after the operation and stayed for four days. Nephrological follow-up was suggested for the patient because of ascending creatinine levels after 48 months. The patient will be observed for 60 months after the operation. Histopathological evaluation of the resected ileum was diagnosed as vasculitis. **Figure 1** shows gross pathologic and microscopic section specimens. The second patient was a 44-year-old male diagnosed with an invasive transitional cell carcinoma after the first TUR-B operation. A radical cystoprostatectomy with a studer neobladder was performed. Blood loss was 850 mL. The postoperative period was uneventful, except for prolonged lymph drainage caused by lymphocele and hypoalbuminemia. Albumin replacement was done for the patient. The patient was discharged seventeen

Table 2. Mortality rate, gastrointestinal and vascular complications of the first 100 patients (mean age: 60.7 years) who were operated in our clinic.

Mortality 4 cases		
Age	**ASA score**	
55	2	Pulmonary embolism
62	2	Septicaemia
81	3	Heart failure
60	3	Pulmonary embolism
Gastrointestinal complications		
8 cases	Evisceration	2
	Subileus	4
	Ileal fistula	1
	Rectum Injury	1
Cardiovascular complications 7 cases		
	External iliac injury	1
	Deep venous thrombosis	3
	Pulmonary embolism	2
	Heart failure	1

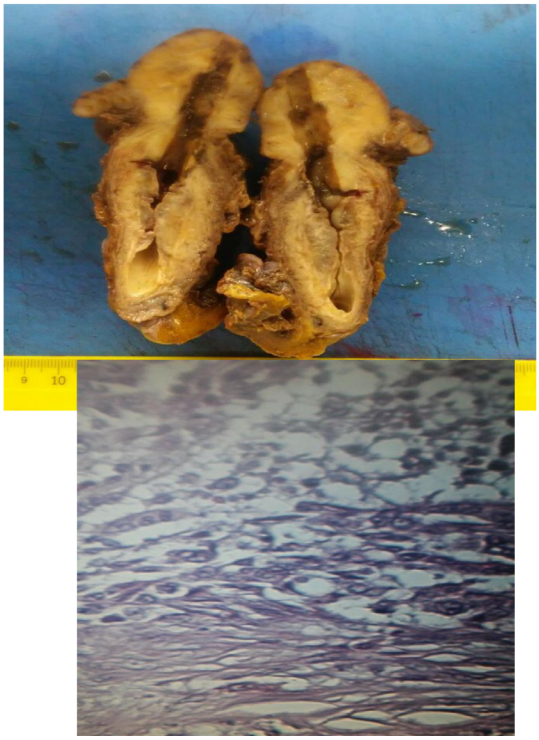

Figure 1. Gross pathology specimen and microscopic section specimen

Table 3. Perioperative and postoperative complications

Case	Blood loss/mL	Transfusion units	Perioperative complication	Postoperative complications 90 < days	Clavien-Dindo classification score	Duration of surgery/minutes
1	500	no	Ileal ischemia,	Urinary infection	I	380
2	850	1 es/iu	None	Prolonged lymph drainage, hypoalbuminemia	II	350
3	2850	7 es/iu	Acute bleeding	Acute bleeding, wound infection, hypokalemia	V (death; acute bleeding)	440
4	3000	7 es/iu	None	Acute bleeding	V (death; acute bleeding)	410

days after the operation. Adjuvant chemotherapy with carboplatin/gemcitabine was administered after the operation. No complications related to BD were observed in this patient. This patient died after 12 months due to tumour progression. **Figure 1** shows gross pathologic specimen and microscopic specimen of this patient. The third patient was diagnosed with an invasive urothelial carcinoma (PT2G3) of the bladder after the first TUR-B operation. This male patient underwent a radical cystectomy with an orthotopic neobladder. The right common iliac artery started to bleed spontaneously after lymph node removal. A cardiovascular surgery consultation was requested, and the arterial tear was repaired using a Dacron patch. Hypokalemia was determined in the first postoperative day and wound infection occurred in the third day. On the seventh postoperative day, spontaneous bleeding occurred from the drain. Urgent operative intervention was carried out. Acute bleeding was detected from the right common iliac artery and resulted in patient's death. The source of the bleeding was the injured segment of the iliac artery where the patch was placed. The patch was separated partially from the iliac artery. A pathological evaluation of the common iliac artery revealed an obliterative vasculitis of the vaso vasorum. For the fourth patient, a radical cystectomy with an ileal conduit was planned. The TUR-B pathology of this patient was PT2G3. The final pathology was PT-2G3N0. On the first postoperative day, hypotension and tachycardia were observed, requiring urgent operative intervention. Cardiovascular surgeons were called for operation who used a Dacron patch on the patient. Afterwards, the patient was transferred to the intensive care station. Ileus and evisceration occurred on the fifth postoperative day. Subsequently, acute spontaneous bleeding occurred. The patient died during urgent operative intervention. The patch was separated from the common iliac artery. Information about complications and the classification of postoperative complications with the Clavien-Dindo score is presented in **Table 3**.

DISCUSSION

BD was described by Hulusi Behçet in 1937; its incidence is higher in the Middle East, Japan and Mediterranean countries. Currently, it is believed that the pathological basis of the disease is systemic vasculitis affecting both small and big vessels[6]. Both sexes are equally affected, but the syndrome is more severe in young men[7]. The authors have reported an increased morbidity in BD patients compared to patients without BD[8]. In contrast, Cengiz et al. reported that the surgical treatment of malignancies in the presence of BD appeared to be safe[9]. Regarding the safety of radical cystoprostatectomy in BD patients, there is only one publication. Baltacı et al. concluded that a radical cystoprostatectomy is safe in patients with BD[10]. They presented the first case of sporadic bladder cancer with BD. This case was a grade 3 transitional cell carcinoma with perivesical invasion and lymph node metastasis (pT3bN1M0). The patient died 6 months after surgery due to tumour progression. Gastrointestinal involvement of BD varies in different populations, and it is reported to be common in Japan; however, the exact prevalence of gastrointestinal involvement in BD is still unknown. Symptoms of gastrointestinal involvement include anorexia, vomiting, dyspepsia, diarrhoea and abdominal pain[11]. The presence of gastrointestinal involvement in BD is not commonly accompanied by clinical symptoms. Köklü et al. reported that only three out of nine patients with ileum ulcers complained of gastrointestinal symptoms. Moreover, they diagnosed abnormal microscopic findings as vasculitis and ileitis in 23 patients without macroscopic findings. The findings of vasculitis and ileitis were significantly higher than in patients without BD. They concluded that ileal visualisation should be performed during colonoscopic examinations in clinical practices to document intestinal involvement[12]. In our case where ileal ischaemia occurred, there was no visible sign of an ulcer or any other pathology during the preparation of the ileum. Likewise, the patient did not complain about any gastrointestinal symptom before the surgery. The reason for acute ischaemia may have been the involvement of the arteries feeding the ileum. We came to the conclusion that the reason for ileal ischaemia was BD involvement; the patient had no other factors, such as cardiovascular disease or atherosclerosis, that could have predisposed the patient to ischaemia. Further, the patient was not one of our first cases, so we can exclude inexperience as a probable factor for this complication. It is known that arteries can cause bleeding, infarction and limb ischaemic symptoms despite immunosuppressant or steroid medication[13]. It should be noted that our patient was only consuming Colchicine at the time of the operation and was not in

the active phase of BD. A colonoscopic evaluation and concomitant biopsy before surgery may be useful in these patients to predict gastrointestinal involvement and the probable risk for perioperative complications.

Regarding vascular manifestations in BD, arterial involvement and aneurysm formation are the most serious complications[13]. The most common site of aneurysm formation is the aorta, followed by the pulmonary and femoral arteries[13]. Cigarette smoking is reported to be a possible risk factor for arterial disease in patients with BD[14]. Recent studies of patients confirm that males and patients with a younger age of disease onset are at a higher risk for vascular involvement[15]. Fatal complications may occur in patients with arterial involvement more frequently than with venous involvement[13-14]. The occurrence of an aneurysm is, together with a mortality rate of up to 60% if it is not treated[16]. In the two cases in our report in which spontaneous vascular bleeding occurred on the common iliac arteries, the time since BD diagnoses was 7 and 11 years. There were no signs of an aneurysm or any visible pathology on the artery during lymph node dissection around the iliac vessels. It should be noted that further evaluation of the cardiovascular system, including CT angiography, MR angiography or Doppler ultrasound, may be helpful in diagnosing vascular disease. In our study, only an enhanced abdominal CT, which revealed no evidence for vascular disease, was requested for our patients. Common iliac artery was probably involved in our two cases, and inflammation caused the vascular wall to weaken without the formation of an aneurysm. The pathology and pathogenesis of the arterial involvement in BD has been documented by Matsumoto et al. They described it as an inflammatory obliterative endarteritis of the vasa vasorum, most likely brought about by immune deposition. It causes destruction of the tunica media and fibrosis, weakening and predisposing arterial wall to aneurysm formation and eventually aneurysm rupture[17]. Smoking cigarettes is another predisposing factor for vascular disease. Both of the patients were long-time smokers. Manipulation of the vessels during lymph node dissection could have stimulated the rupture of these weak vessel walls. Another important point is that during lymph node dissection, the surgeon did not observe evidence of injury to the vessels. Regatding the treatment of vascular complications in BD, various endovascular or surgical interventions have been performed in patients with BD. Nevertheless, the outcomes of endovascular and surgical intervention are still unfavorable[18,19]. Kwon et al. presented their results of surgical treatment for abdominal aneurysms in BD. They concluded that resection and interposition grafting revealed much better results than a patch closure. The recurrence rate of patch closure (62.5%) was significantly higher than the rate of an interposition graft (14.3%). At least one patient with a patch closure died due to a recurrent aneurysm after 4 months. Authors declared that surgical treatment for arterial involvement of BD is highly associated with postoperative complications; therefore, the surgical treatment should not be applied in the active phase of the disease, and systemic therapy, including aspirin and corticosteroids, should be considered for all patients[20]. Furthermore, another study reported that remission using glucocorticoid before surgical intervention can decrease the incidence of postoperative anastomic complications[21]. Interestingly, none of our cases were in the active phase of BD, and the patients were on prednisolone therapy. Nevertheless, acute bleeding occurred, and the patches were separated spontaneously from the common iliac arteries. After our experience with four bladder cancer patients with concomitant BD, we conclude that radical cystoprostatectomy shows higher morbidity and mortality in these patients. It should be emphasised that all patients were in the inactive phase of the disease. In this context, detailed preoperative evaluation related to BD should be performed. Ileal visualisation, including microscopic evaluation, could be done to determine potential ileal involvement (if an ileal reservoir is planned to be used). CT angiography or Doppler ultrasonography are preferred modalities for vascular evaluation. We suspect that the sufficiency of these methods to establish vascular involvement is efficient because we are able to detect pathology on the arteries during operation or on CT. Strict cooperation with the rheumatology department and cardiovascular surgeons is required before deciding for an intervention on BD patients.

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