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Treatment of Bladder Cancer: Anti-PD-1 Drug Treatment Associated Hypothyroidism

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1. Abstract

Bladder cancer is a common malignant disease of the urogenital tract, and over the past few decades, immunotherapy, based on the principle of activating the patient's immune system to root out malignant cells, has largely changed the treatment of cancer. Anti-PD-1 drugs include monoclonal antibodies against PD-1 and the PD-1 ligand (PD-L1). Tislelizumab is a humanized IgG4 anti-PD-1 monoclonal antibody that is indicated for the treatment of locally advanced or metastatic PD-L1 high expression uroepithelial carcinoma (UC) in patients who have failed platinum-containing chemotherapy, including neoadjuvant or adjuvant chemotherapy within 12 months of progression. Immunotherapy works as a drug that boosts the body's natural defenses against cancer. These drugs have adverse effects, collectively referred to as immune-related adverse events, that represent immune effects on normal tissues that may result from stimulation of the immune system. Hypothyroidism is one of the organ-specific immune-related adverse events. We present the case of a 55-year-old man who was diagnosed with bladder cancer caused hypothyroidism after treatment with conventional chemotherapy drugs in combination with tislelizumab.

2. Introduction

The genitourinary system includes the genital organs and the urinary system. The latter includes the kidneys, ureters, and the bladder, which is the only pelvic cavity (Figure 1). The bladder is a hollow organ, and urine in the bladder is discharged through the urethra when the muscles contract [1]. Bladder cancer (BC) is the second most common malignancy of the urogenital tract and the 10th most common cancer, usually affecting the elderly, with a peak age of onset of 70-80 years [2]. It is more common in men than women and about 4 times more common in women worldwide. As a result, the disease ranks higher among men, for whom it is the 6th most common cancer and the 9th leading cause of cancer death [3]. The geographic and temporal patterns of observed global bladder cancer incidence appear to reflect the prevalence of smoking, although infection by schistosomiasis (in North Africa and parts of sub-Saharan Africa) and other risk factors (occupational exposure to aromatic amines and other chemicals affecting workers in the painting, rubber, or aluminum industries, and arsenic contamination in drinking water) may be a major cause in some populations [4]. As smoking rates have risen among women, rates have stabilized or declined among men, but

there have been some upward trends among women. In the United States in 2014, an estimated 39 percent of bladder cancer cases in women were attributed to smoking, compared to 49 percent in men. Mortality rates have declined in developed countries, partly due to improvements in treatment (e.g., endoscopic resection, adjuvant chemotherapy, and intravesical immunotherapy) [5, 6]. Bladder cancer is classified according to cell type and stage of tissue invasion. Besides urothelial carcinoma/transitional cell carcinoma (UC/TCC), which is by far the most common type of bladder cancer (90-95%), other malignancies as squamous cell carcinoma (2-5%), adenocarcinoma (0.5 2%), and small-cell carcinoma (<1%) all describe tumors of the bladder. Although UC/TCC occurs primarily in the bladder, the ureter and urethra can also be affected [7]. In general, UC is classified as either non-muscle-aggressive bladder cancer (NMIBC), which accounts for about 75% of cases, and muscle-aggressive bladder cancer (MIBC), which accounts for about 25% of patients [8, 9]. Both were further staged using tumor, Nodule, metastasis (TNM) classification. This describes how much the tumor has grown (T), whether the cancer has spread to nearby lymph nodes (N), and whether it has begun to metastasize (M). Ta describes a non-invasive papillary carcinoma that is confined to the mucous membrane, growing from the lining (urothelium) to the bladder cavity. Tumors that grow flat on the urinary skin, do not invade connective tissue, and do not extend into the lumen are classified as carcinomas in situ (CIS), called Cis/Tis. Papillary tumors that invade the lamina propria and connective tissue are classified as T1. Ta, Tis, and T1 are classified as NMIBC, while stage ≥T2 is classified as MIBC. In T2a or T2b, the cancer has invaded the medial or lateral pushing and pulling muscles, and in T3, the tumor has invaded the muscle layer and surrounding fat tissue. In T4, the tumor has begun to grow through the bladder wall into the pelvic or abdominal wall, invading adjacent organs and/or beginning to spread to nearby lymph nodes or even further away organs (metastasis, M1) (Figure 2).

After diagnosis and tumor staging, NMIBC tumors are stratified by the risk of recurrence and/or progression: while lower grade tumors consist of slower growing, more differentiated cells, higher grade tumors are poorly differentiated and tend to spread faster. In addition, lower grade tumors have a lower risk of recurrence, while higher grade tumors have a higher risk of progression and metastasis. Doctors have several options to diagnose UCs. However, cystoscopy is considered a key diagnostic tool for bladder cancer. To assess the cell type and stage of tissue invasion, a transurethral resection of the bladder (TURB) is performed to confirm the diagnosis and the correct stage of the patient. All papillary tumors are completely removed during TURB, and in some cases, this can be considered a treatment. CIS cannot be completely removed during TURB, so additional indoctrination therapy is required to reduce tumor burden, recurrence, and/or progression. For high-risk and moderate-risk NMIBC patients, there is evidence that relapse rates can be significantly reduced by administering additional chemotherapy drugs to the bladder (such as mitomycin c) or Bacillus Calmette Guérin (BCG)[10, 11]. The primary treatment of patients with MIBC depends on the M (metastatic) status. For local MIBC (M0), the primary and standard treatment is complete removal of the bladder and production of urinary shunt (root cystectomy) +/- neoadjuvant therapy. 10-15% of patients with muscular invasive diseases have metastases at the time of diagnosis [11]. As first-line therapy in advanced stages, platinum-based chemotherapy drugs, such as cisplatin, interfere with DNA replication in rapidly growing cells [12]. In addition, intravenous administration of the nucleoside - analogue gemcitabine, structurally related to cytidine, and infusion of mitomycin c is a chemotherapy treatment regimen [13]. Although bladder cancer is relatively sensitive to chemotherapy, recurrence after first-line treatment with the chemotherapy drug gemcitabine plus cisplatin leads to a poor prognosis [14]. If treatment fails, a cystectomy may be required, in which the bladder is partially or completely removed [15]. Since this is a radical measure with a significant impact on patients' quality of life, new treatment options are necessary, allowing for more precise treatment and circumventing the side effects observed in classical chemotherapy. Over the past few years, immune checkpoint suppression has had a huge impact on cancer treatment. In particular, antibodies that block the interaction of programmed cell death protein 1 (PD-1) and its ligand (PD- L1) have shown impressive results in clinical applications. PD-1 monoclonal antibodies currently approved by the FDA include Pembrolizumab, Nivolumab, and Cemiplimab, and PD-L1 monoclonal antibodies include Attilizumab, Duvaliumab, Avalumab. With the exception of Cemiplimab, all of these anti-PD -(L)1 antibodies are used for UCs[16, 17]. In addition to Pembrolizumab, Nivolumab, Atezolizumab and Durvalumab, PD-1 monoclonal antibodies developed in China including Camrelizumab, Tislelizumab, Sintilimab and Toripalimab are currently approved by China's National Medical Products Administration (NMPA). Tislelizumab is approved for use in UCs. Studies of PD-1 and PD-L1 expression in UC samples have showed elevated levels of PD-(L)1 expression in high-risk UCs compared to low-risk UCs[16]. Immunohistochemical results of surgically resected UC specimens showed that PD-L1 expression was found in 21.1% of cases[18]. In addition, PD-L1 expression is associated with tumor invasion of monocytes[19]. Another study found that PD-L1 is an important prognostic factor for postoperative recurrence and survival[18]. The anti-PD-L1 mAb Atezolizumab (Tecentriq) was the first MIBC checkpoint inhibitor to be approved in 2016[20]. Since then, The U.S. Food and Drug Administration (FDA) has approved PD-1- specific mAbs Nivolumab (Opdivo)[20] and Pembrolizumab (Keytruda)[21] and PD-L1-targeting antibodies Avelumab (Bavencio)[20, 21] and Durvalumab (Imfinzi)[21, 22] for locally advanced or metastatic

UC showing tumor progression during or after adjuvant therapy utilizing platinum- containing chemotherapy or neoadjuvant treatment in. Today, PD-1/PD-L1 specific antibodies became the standard of care as a second-line treatment for bladder cancer patients. Immunotherapy can boost the body's natural defenses against cancer, but at the same time these drugs have adverse effects, collectively referred to as immune-related adverse events, representing the immune effects of the drug on normal tissue, which can occur due to stimulation of the immune system[23]. Immune-related adverse events caused by immune checkpoint inhibitors are unique in terms of the organs involved, mode of onset, and severity, compared to toxicities caused by conventional treatment modalities (chemotherapy, radiotherapy, and their combinations) [24]. The toxicity of anti-PD-1 drugs was generally lower than that of standard chemotherapy, but immune-related adverse events were reported in clinical follow-up. Organ-specific immune-related adverse events, including colitis, hepatitis, pneumonia, and hypothyroidism, are common, as are more general adverse events related to immune activation, including fatigue, diarrhea, and rashes[25-30]. We present the case of a 55- year-old man who was diagnosed with bladder cancer caused hypothyroidism after treatment with conventional chemotherapy drugs in combination with Tislelizumab.

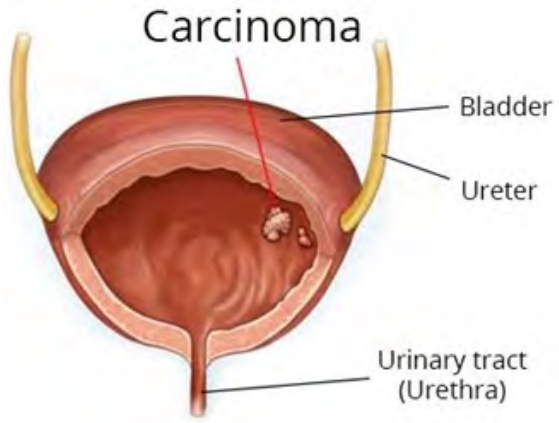

Figure 1

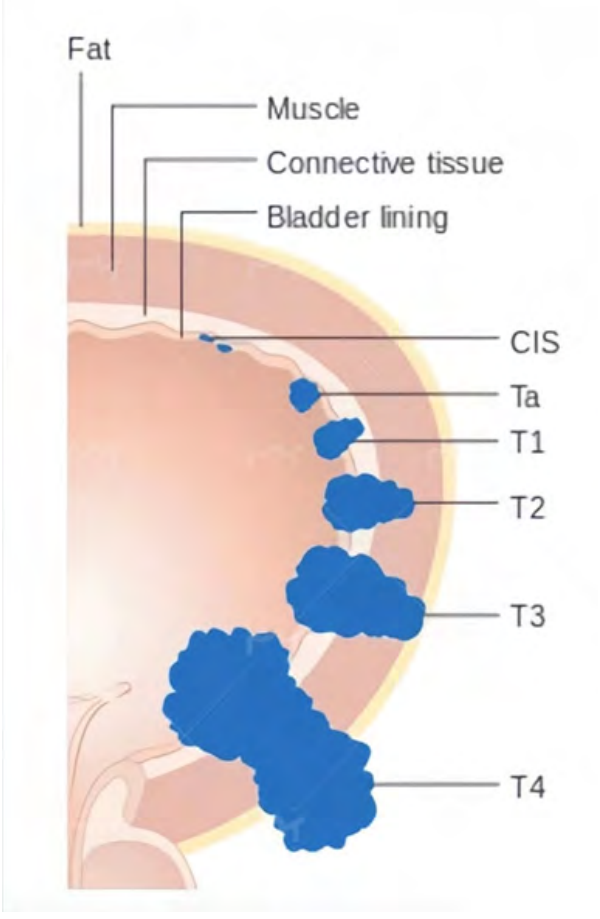

Figure 2

3. Case Presentation

The patient self-reported that in 2022, due to “low back pain, frequent urination and incontinence”, he was considered in the local hospital for urinary tract infection (high possibility of acute pyelonephritis). After 2 weeks of treatment with oral antibiotics (specific details are unknown), the symptoms did not relieve, and the color Doppler ultrasound examination of the urinary system indicated space-occupying lesions. After further improvement of pelvic MR, the possibility of bladder malignant tumor was considered to be high. Transurethral resection of bladder tumor was performed on August 31, 2022. Postoperative pathological results revealed that high-grade urothelial carcinoma was invasive in the bladder, invading the proper muscle layer, and invasive growth of high-grade urothelial carcinoma was seen in the tumor and the fibrous connective tissue and skeletal muscle tissue with hyperplasia. Subsequently, the patient received neoadjuvant therapy in the Third Medical Center of the PLA General Hospital with GC+ Tislelizumab for a total of 4 cycles. In June 2023, ultrasound examination was performed again, indicating bladder tumor recurrence, and neoadjuvant tumor therapy was decided again in a local hospital for 2 cycles. Nuclear medicine (PET/ CT) examination was performed in our hospital on December 5, 2023, indicating: Compared with the examination on August 11, 2022: 1. The postoperative review of bladder cancer showed that the bladder wall of the operative area was hairy and the metabolism increased. Please combine cystoscopy to exclude the possibility of recurrence. 2. The left kidney is slightly smaller with parenchyma thinning, and the tracer concentration is not good, suggesting impaired renal function; Dilated fluid in the upper middle section of both ureters.

4. Previous History

The patient has a history of hypertension for more than 10 years and was treated with nifedipine, telmisartan and other drugs orally. A 1-year history of coronary heart disease without drug treatment. In early December, she was diagnosed as hyponatremia due to lethargy and unconsciousness, and her condition improved after symptomatic treatment. In the past, due to bone marrow depression after chemotherapy, platelet and hemoglobin decreased for many times, and intravenous transfusion of apheresis platelets and suspended red blood cells. The patient’s further improvement of abdominal CT examination suggested: 1. Uneven thickening of the left posterior wall of the bladder, combined with the history, was considered to be a recurrence of bladder cancer. 2. Abnormal prostate changes, consider: calcification of prostate hyperplasia. 3. Left ureter and upper pelvis hydrops. After full consideration and discussion, robotic left nephro- ureterectomy + radical cystectomy + ileal passage under general anesthesia was performed on January 3, 2024. The specific surgical procedures are as follows: After successful anesthesia, the right reclining 60-degree position was taken, and the surgical field was routinely disinfected and covered. Pneumoperitoneum was established transumbilically and trocaT was implanted to connect Da Vinci surgical robot. Open the left lateral peritoneum and open the left half of the colon inwards. The posterior peritoneum was separated from the perineal fascia space, the left kidney fat pocket was exposed, and the perineal fat shock was dissociated from the ventral, dorsal and lower poles respectively. It is divided between the genital vein and the ureter to the psoas major plane. Lift the kidney. The ionization was continued on the cephalic side until the level of the left renal artery. The left renal artery was clipped with surgical clamp. Left renal vein was treated in the same way. The ipsilateral adrenal tissue was retained, and then the left perirenal tissue and left full-length urethral duct were completely free to the iliac blood vessel level. The left kidney and ureter were pulled to the left iliac fossa, and a latex drainage tube was placed in the left renal area. Re-abduction of both legs to lithotomy position. The F16 catheter was placed on the platform and the chemotherapy drug pirarubicin was injected. Pneumoperitoneum was re-established and trocar was started. The Da Vinci surgical robot was connected to cut the posterior peritoneum at the left general bifurcation, and the left ureter was found and freed to the bladder wall. The right side was treated in the same way. Empty the bladder, lift the bladder forward with the separation forceps to reveal the vesicorectal fossa, cut the peritoneum at the fold, and find that the texture of the seminal vesicle is harder than that of the normal seminal vesicle, and tumor invasion is possible. Carefully free the vas deferens, seminal vesicle and posterior prostate wall. The lateral peritoneum was cut along the lateral umbilical ligament of the left side, and it was found that the left bladder wall was heavily adhered to the pelvic wall. The space between the bladder and the left abdominal wall was carefully separated, the lateral pedicle of the bladder was exposed, and the lateral pedicle of the bladder was severed

After Hem-o-lok clamp, and the right side was treated in the same way (the right-side adhesion was light). Cut the median umbilical ligament and enter the retropubic space. The puboprostatic ligament was separated, exposed and severed, the pelvic floor fascia was cut on both sides, and the dorsal vascular complex of the penis was sewed with 3-0 barb line. The right ureter was severed outside the bladder wall. The lateral prostatic ligaments were separated and severed by extrafascial technique. The urethra was severed under the sewed back vascular complex of the penis, and the urinary tract was separated from the prostatic tip. The urinary tube was removed, and the proximal end of the urethra was cut off with a large Hem- o-lok. Lymph node dissection was performed. First, fat and lymph tissue around the right external artery and paratobturator were removed, up to the bifurcation of the abdominal aorta. The dissection of the left pelvic lymph node showed that the left pelvic lymph node region was heavily adhesively attached. Considering that forced dissection was more likely to damage the iliac blood vessels, the dissection of the left pelvic lymph node was terminated. The right catheter was separated

from the lower pole of the kidney, and the excised left kidney and the catheter, bladder, prostate, fine flower and neoplasms were put into a specimen bag. Reconstruction: No abnormality was found in the ileocolon, ascending colon and mesangium. A longitudinal incision was made 8cm below the umbilicus and specimens were removed. The right ureter and ileum were removed. A linear cutter was placed on the ileum 15 cm away from the ileocecal part, avoiding the mesenteric vessels. The ileum of 15 cm was selected, the intestinal tube was cut with a linear cutter, and the intestinal continuity was restored with Overlap, and the serosal muscle layer was discontinuous and sutured. F7 single "J" tube was inserted into the ureter through the ileal channel, and the right ureter and the proximal end of the ileal channel were anastomosed by Bricker method. 3-0 Absorbable sutures secure a single "J" tube on the ileum. A circular incision was made through the rectus abdominis muscle on the right anterior superior iliac ridge and umbilical line, with a diameter of 1.5cm, and the subcutaneous fat inside the incision was removed. The anterior sheath of rectus abdominis was dissected, the rectus abdominis bundle was separated, and the rectus abdominis incision was bluntly expanded through the posterior sheath of rectus abdominis and peritoneum. The ileum passage was removed from the rectus incision through the body with intestinal forceps. The outer edge was about 1cm higher than the abdominal wall. The ileum passage was fixed with the anterior sheath of rectus abdominis at 0, 3, 6, and 12 o 'clock, and the distal end was sewed into a nipple and fixed with the abdominal wall. A latex drainage tube was placed in the ileal passage and fixed with a ureteral stent. A pelvic silicone drainage tube was placed in the auxiliary hole of the abdomen and fixed. The procedure was smooth and the bleeding was about 300ml. 2 units of red blood cells (300ml) were transfused during the operation. However, the patient had difficulty recovering from anesthesia and was transferred to surgical ICU for further treatment. Retrospective examination of the patient before admission showed that PET/CT indicated thyroid deficiency and no abnormal radioactive concentration was observed. The patient denied any previous history of hypothyroidism or thyroid surgery. The patient's completed thyroid function test results (Table 1) indicated hypothyroidism, and the endocrinology department was requested to assist in diagnosis and treatment. Considering that the patient had a history of PD-1 drug use after immunotherapy for bladder cancer, it was considered that the patient had immune-related hypothyroidism. Considering that the patient's poor recovery after anesthesia was related to hypothyroidism, the patient was given 50ug levothyroxine sodium tablets daily, and the patient gradually became conscious.

Table 1: Thyroid Function Test

Test Item	Result	Unit	Reference Range
Thyroid stimulating hormone (TSH)	>51.600 ↑	uIU/ml	0.38-5.33
Serum free thyroxine (FT4)	6.790 ↓	pmol/L	7.64-16.03
Serum total thyroxine (TT4)	85.710 ↓	nmol/L	69.97-152.52
Serum free triiodothyronine (FT3)	2.110 ↓	pmol/L	3.28-6.47
Serum total triiodothyronine (TT3)	0.200 ↓	nmol/L	1.01-2.48

5. Discussion

As the use of anti-PD-1 drugs increases, non-oncologists will increasingly be called upon to manage rare but clinically important organ- specific immune-related adverse events as well as the more common general adverse events associated with immune activation [23]. Currently, many cancer patients are primarily treated by oncologists and may lose contact with other doctors. This model of care may poorly serve patients treated with checkpoint inhibitors, whose cancer may still be under control but where various adverse events may threaten health and quality of life. Multidisciplinary clinical teams can better meet the long-term needs of these patients, although the best clinical and care delivery methods for early detection and appropriate management of immune-related adverse events are evolving and require further investigation [31, 32]. Just like the hypothyroidism reported in this case, for such patients using anti-PD-1 drugs, we should also regularly monitor the changes in thyroid function of the patients, and timely communicate with the endocrinologist to adjust the medication plan, especially for patients with surgical needs.

Anti-PD-1 drugs can achieve long-term tumor control through long- term immune activation, so immune-related adverse events that need to be managed may persist, progress, or even emerge over time. A better understanding of long-term adverse events with monoclonal antibodies is essential to optimize the delivery of care. Phase 4 studies are often recommended to enhance understanding of long-term adverse events of newly approved drugs, although they are rarely conducted and are time- consuming. Given that the number of patients treated with anti-PD-1 drugs is expected to grow rapidly, institutional cohort studies can provide more direct insights into immune-related adverse events, highlighting

not only short-term but also long-term adverse events. In addition, investigators should publish updated adverse event information as well as cancer outcomes as they report longer follow-up from earlier checkpoint inhibitor studies. Only a small amount of this data is publicly available [33]. For the patients reported in the article, currently the patients can only rely on exogenous thyroid hormone supplementation to maintain the homeostasis of thyroid function, but the current drug instructions do not mention whether the thyroid function of such patients is possible to recover after drug withdrawal and the specific recovery time. Therefore, we also need to continue further follow-up of such patients, observe the self-recovery of thyroid function in the follow-up of patients, adjust the dosage in time, and provide a direction for clinical diagnosis and treatment. At the same time, when severe immune-related adverse reactions are encountered, whether the oncologist should stop using the drug also deserves further research and the development of corresponding standards.

6. Conclusion

Anti-PD-1 drugs increase the risk of organ-specific immune-related adverse events, such as hypothyroidism, compared to standard treatment. Therefore, we need to closely monitor the changes in thyroid function of patients after medication.

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