＜泌尿器科＞

① Laparoscopic resection of a retroperitoneal ancient schwannoma: a case report and review of the literature.

② Yoshino Tateki, Yoneda Kenji

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④ Anticancer Research

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Laparoscopic Resection of a Retroperitoneal Ancient Schwannoma: A Case Report and Review of the Literature

TATEKI YOSHINO and KENJI YONEDA

Department of Urology, Mazda Hospital, Hiroshima, Japan

Abstract. *Schwannomas are benign tumors that arise from neural sheath Schwann cells. Solitary benign schwannomas are generally located in the head and neck, often along the cranial nerves, and are a particularly rare neoplasm among tumors of the retroperitoneal space. A 67-year-old man undergoing a general health check was incidentally found to have a mass beside the left kidney. Computed tomography (CT) revealed a cystic adrenal mass located cephalad to the left kidney. Retroperitoneoscopic resection of the retroperitoneal mass was performed. The pathological diagnosis was retroperitoneal benign schwannoma consisting of mixture of a Antoni-A and -B type cells. We report a case of retroperitoneal schwannoma and discuss eleven previous reports treated by laparoscopic surgery in the English literature. Laparoscopic resection may be useful because a retroperitoneal schwannoma, which is commonly localized and hypovascular, can easily be dissected from the adjacent tissues.*

Schwannomas are tumors of the nerve sheath that usually exhibit benign behavior and are found in all organs and in the nerve trunk, although rarely in the retroperitoneum, since these comprise only 3% of all schwannomas (malignant and benign combined) (1). Ancient change in a schwannoma (ancient schwannoma) is a relatively uncommon histological variant characterized by degeneration. The term ancient schwannoma was first suggested by Ackerman and Taylor (2) in a review of 48 neurogenic tumors of the thorax. They reported 10 cases that showed similar features of a typical neurilemmoma, but were distinctive because significant portions of these tumors were composed of only a few cells within a hyalinized matrix. They clarified that these features occurred in the schwannomas of long duration and hence coined the term 'ancient schwannoma'. This type is characterized by diffuse areas of hypocellularity, focal accumulations of hyaline material, and fatty degeneration (3). We report a case of retroperitoneal ancient schwannoma that was discovered incidentally in a patient by abdominal ultrasonographic examination and resected successfully by laparoscopic surgery.

Correspondence to: Tateki Yoshino, M.D, Department of Urology, Mazda Hospital, 2-15 Aosaki-minami, Fuchu-cho, Akigun, Hiroshima, Japan, 735-8585. Tel: +8 1825655000, Fax: +81 825655138, e-mail: uroltateki@yahoo.co.jp

Key Words: Schwannoma, laparoscopic surgery, retroperitoneum, S-100 protein.

Case Report

A 67-year-old man had a left renal mass that was found incidentally on abdominal ultrasonography (US) during a medical health checkup and was referred to our institution for additional evaluation. His medical and family histories were unremarkable. At the initial examination, his blood pressure was 132/80 mmHg. Biochemical results, carcinoembryonic antigen, carbohydrate antigen 19-9 and interleukin-2 receptor were all within the normal ranges, including serum catecholamines. CT revealed a well-defined round 80×75×60 mm cystic mass with a rim of soft tissue in the left adrenal region. There were neither calcifications nor evidence of infiltration. Enhancement of the peripheral rim of soft tissue was seen after intravenous administration of contrast material (Figure 1). Magnetic resonance imaging (MRI) showed a smooth marginated low-intensity mass on T1-weighted image and high-intensity on T2-weighted image. Adrenal scintigraphy using ^{131}I-adosterol and ^{123}I-metaiodobenzylguanidine (MIBG) did not show increased activity in the region of the mass. A tentative preoperative diagnosis of a malignant tumor of undetermined origin, schwannoma, nonfunctioning pheochromocytoma or paraganglioma was considered on the basis of the imaging and laboratory results. The patient underwent left adrenalectomy, during which the surface of the tumor was found to be smooth and slightly adherent to the left kidney. The resected specimen was oval and firm; it measured 83×65×45 mm and weighed 147 g. The tumor was well demarcated from the adrenal gland and the cut surface of the excised specimen exhibited red-brownish cyst formation and a yellowish-white rim (Figure 2). Pathological examination showed whorls and interlacing fascicles of schwannoma spindle cells, along with alternating

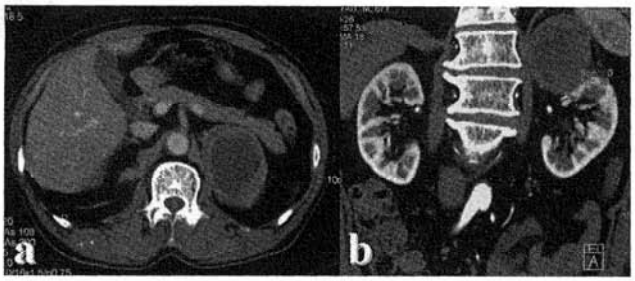

Figure 1. *Computed tomography showed a well-defined round, 80×75×60 mm cystic mass with a rim of soft tissue in the left adrenal region. Slight enhancement of the peripheral rim of soft tissue was seen after intravenous administration of contrast material. (a: Axial image, b: coronal image).*

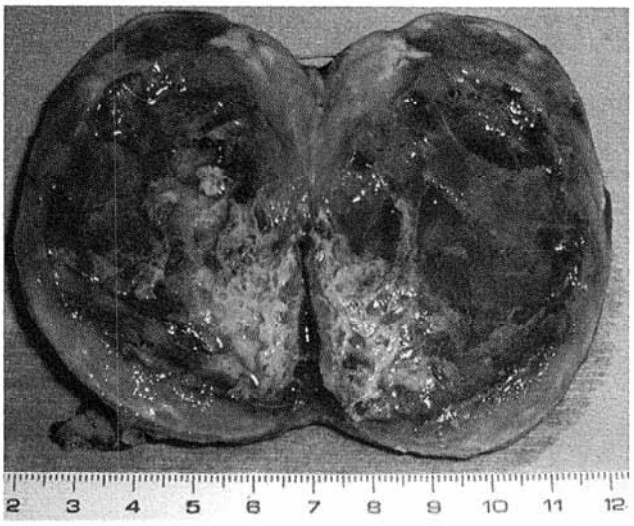

Figure 2. *The cut surface of the excised retroperitoneal mass showed red-brownish cyst formation and a yellowish-white rim.*

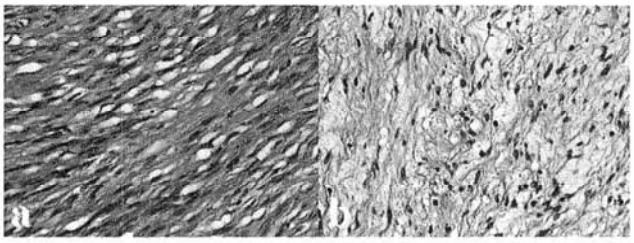

Figure 3. *Pathological findings (×400) of the retroperitoneal mass revealed compact cellular lesion (a: Antoni type A tissue) and loose, hypocellular, myxoid lesions with microcystic spaces (b: Antoni type B tissue).*

Antoni-A and -B patterns with areas of hyalinization and fibrinoid degeneration (Figure 3). Some of the tumor cells were nuclear atypical, but lacked mitotic figures. Immunohistochemical analysis for S-100 was positive. These findings were consistent with the diagnosis of benign ancient schwannoma. Furthermore, no adrenal tissue was found in the specimen, which suggested that the tumor had an extraadrenal origin.

Discussion

Schwannomas are tumors of the nerve sheath of Schwann cells and may arise along the course of any myelinated nerve, with the vestibulocochlear nerve being the most frequent site. These tumors are usually encapsulated, present as a solitary mass and have a benign course (4). These tumors can vary from firm, solid masses to fluctuant cysts. The occurrence of a retroperitoneal schwannoma is rare, comprising only 1-3% of all schwannomas (1) and only 1% of all retroperitoneal tumors (5). Retroperitoneal schwannomas occur most commonly in patients between forty and sixty years of age, with a male:female ratio of 2:3 (6). Because they are usually slow-growing and asymptomatic, retroperitoneal schwannomas are often found incidentally, as in the present case (7). Although patients with a retroperitoneal schwannoma are usually asymptomatic, some present with vague and nonspecific abdominal or back pain.

Laboratory data for schwannoma are generally not remarkable or contributory to its diagnosis. Histologically, schwannomas consist of compact cellular lesions (Antoni type A tissue) and loose, hypocellular, myxoid lesions with microcystic spaces (Antoni type B tissue). In addition, almost all schwannomas show intense immunohistochemical staining for S-100 protein, confirming the neuroectodermal origin of the tumor cells (8).

An ancient schwannoma is a rare variant first described by Ackerman and Taylor (2) and is characterized by degenerative changes and diffuse hypocellularity. A benign schwannoma is depicted as a well-defined and inhomogeneous low-density mass on CT scan images, while MRI is able to demonstrate the tumor location and its relationship to surrounding structures. MRI of benign schwannomas typically shows hypointensity on T1-weighted images and hyperintensity on T2-weighted images; although this was noted in only 57% of previous cases (5).

A definitive diagnosis is based on pathological, histological and immunohistochemical findings. A preoperative diagnosis is very difficult to make because of the lack of typical imaging features (US, CT and MRI). However, radiological imaging is helpful in treatment planning because it provides information about tumor size, location and possible invasion of other structures. Fine-needle aspiration biopsy may be useful if Schwann cells are found in the sample, but tissues for diagnosis are often inadequate and may be misleading because of cellular pleomorphism in degenerated areas that can be interpreted as malignancy (9). Surgical excision is considered the

treatment of choice for these tumors, which respond poorly to radiation and chemotherapy. Furthermore, there is the possibility of local recurrence and malignant change in benign schwannomas despite prior benign diagnosis (10). Therefore, it is very important to remove the tumor completely. Resection of the tumor under laparoscopic surgery may be performed more completely and easily than under open surgery, because the surgical view under laparoscopy is magnified. To our knowledge, to date, only eleven reports of retroperitoneal benign schwannomas resected by laparoscopic surgery have been reported in the English literature. No cases were definitively diagnosed as schwannoma during preoperative examinations. From available data, the average size of tumors, operation time and intraoperative blood loss including our case were 45 mm (19-80) in maximum diameter, 174 minutes (90-300) and 150 ml (15-310), respectively. There were no severe operative or postoperative complications in almost all cases. Our case had an uneventful postoperative course and was discharged from our hospital on the tenth postoperative day.

In accordance with previous reports, our report shows that laparoscopic surgery is very useful, safe and feasible for the removal of retroperitoneal schwannoma for diagnosis and treatment with minimal invasiveness and rapid postoperative recovery.

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① G－CSF産生膀胱癌の1例　－本邦症例の検討を加えて－

② 吉野干城、米田健二

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④ 泌尿器科紀要

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G-CSF 産生膀胱癌の1例

—本邦症例の検討を加えて—

吉野　干城，米田　健二

マツダ株式会社マツダ病院泌尿器科

URINARY BLADDER CANCER PRODUCING GRANULOCYTE-COLONY STIMULATING FACTOR: A CASE REPORT AND REVIEW OF THE LITERATURE

Tateki Yoshino and Kenji Yoneda

The Department of Urology, Mazda hospital, Hiroshima, Japan

We report a case of urinary bladder cancer that produced granulocyte-colony stimulating factor (G-CSF). A 56-year-old man was admitted to our hospital with the chief complaint of macroscopic hematuria. Cystoscopy demonstrated a thumb tip-sized bladder tumor. Computerized tomography and magnetic resonance imaging showed muscular invasion in the bladder, but no distant metastases. The complete blood count and laboratory examination showed leukocytosis of 25,200/mm^3 and a high G-CSF level of 145 pg/ml in the peripheral blood. Although he underwent total cystectomy and adjuvant chemotherapy using methotrexate, vinblastine, doxorubicin and cis-platinum (M-VAC) under the diagnosis of locally advanced bladder cancer, he died of progressive disease of the carcinoma about eight months after the diagnosis. A temporary decrease of white blood cell count and serum G-CSF were observed just after treatment. The histopathological diagnosis was undifferentiated giant and spindle cell carcinoma of the urinary bladder (grade 3, pT3b, pN1). The tumor cells exhibited positive staining for G-CSF immunohistochemically.

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Key words: Bladder cancer, Granulocyte-colony stimulating factor

緒　　言

G-CSF 産生膀胱癌は比較的稀有な疾患で通常の膀胱尿路上皮癌に比較し，未分化な組織像を示す割合が高く，ゆえにきわめて予後不良と報告されている．調べえたかぎり G-CSF 産生膀胱癌の本邦における報告例は現在までに63例（会議録含む）であり，自験例が64例目である．今回，われわれは G-CSF 産生膀胱癌の1例を経験したので報告する．

症　　例

患者：56歳，男性

主訴：肉眼的血尿

家族歴・既往歴：特記すべき事項なし

現病歴：2006年9月 無症候性肉眼的血尿を主訴に当科受診．画像検査および膀胱鏡検査所見より浸潤性膀胱腫瘍の疑いで，翌月に精査加療目的で当科入院となった．

入院時現症：身長 159 cm，体重 55 kg，体温 37.4°C，血圧 130/95 mmHg，脈拍95/分．体格は中等度であり，胸・腹部に異常所見を認めなかった．

入院時一般検査：末梢血液像 WBC 25,200/mm^3 (Neutro 74.0%，Baso 1.1%，Eos 11.5%，Mono 3.0%，Lymph 10.4%)，生化学検査 CRP 3.59 mg/dl，その他に異常所見は観察されなかった．尿検査では，赤血球 40～60/HPF を認め，尿細胞診は class Ⅲ であった．血清 PSA 値は 0.67 ng/ml と基準値範囲内であった．

膀胱尿道鏡検査所見：尿道に異常所見は観察されず．膀胱右三角部を中心に母指頭大強，広基性，非乳頭状腫瘍が認められた．左尿管口に異常所見はなかったが，右尿管口の同定は不可能であった．

MRI，CT 検査所見：骨盤部 MRI 検査（T2WI）(Fig. 1) では右三角部付近に 25×20×30 mm 大の広基性腫瘍を認め，その基部では固有筋層の断裂および外側の壁不整所見が観察され，膀胱周囲脂肪織浸潤が疑われた．造影 CT 検査では上記膀胱腫瘍に起因すると思われる右水腎水尿管が認められた．また，明らかな遠隔転移を疑う所見はなかった．

臨床経過：2006年10月に経尿道的膀胱生検を施行した．病理組織学的検査所見では，多形性を示す異型上皮細胞の充実性あるいは孤立性浸潤所見が観察され，urothelial carcinoma，G3 の診断に至り，きわめて低分化であった．膀胱頸部および前立腺部尿道の生検組

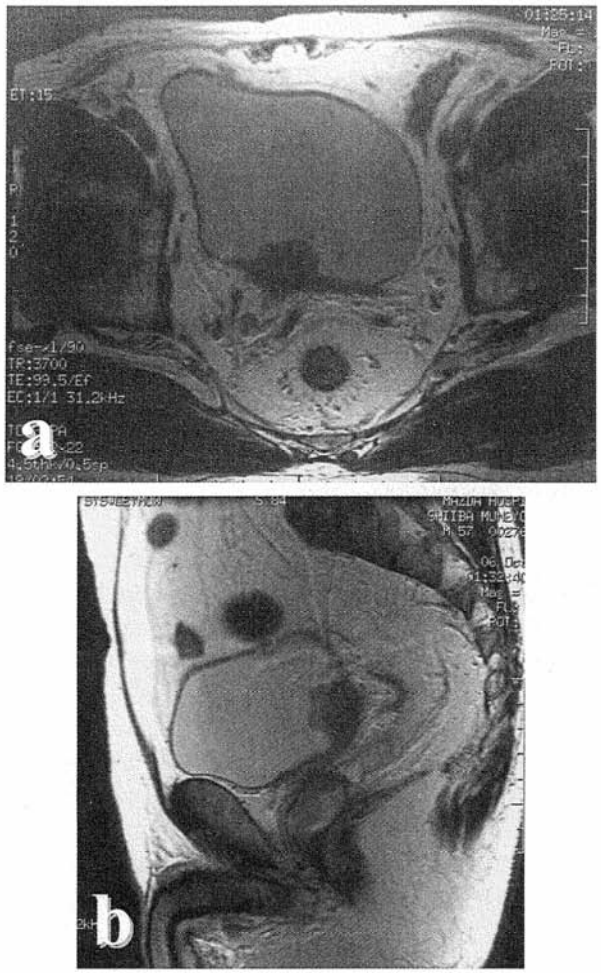

Fig. 1. a : transverse section b : sagittal section Magnetic resonance imaging (T2WI) shows a 25×20×30 mm mass at the right trigone of the urinary bladder. It is speculated that the vesical mass invaded to the perivesical fat.

織より悪性所見はみられなかった．その後，38°C 前後の発熱，20,000～30,000/mm^3 の白血球増多を認めたが，CRP の上昇がなく，血中 G-CSF 値を測定したところ，145 pg/ml（基準値 30 pg/ml 以下）と高値を示したため，G-CSF 産生腫瘍を疑った．

浸潤性膀胱癌 T3bN0M0 の診断にて，2006年12月に膀胱全摘除術および回腸新膀胱造設術を施行した．術中所見では，特に周囲組織との癒着は顕著ではなく，前立腺，膀胱を一塊に摘出した．尿路変向は 60 cm の回腸を使用し，Studer 変法にて新膀胱を造設，回腸尿管吻合は Nesbit 法に準じて行った．病理組織学的検査所見では，大型多角形や紡錘形をなすきわめて未分化な異型細胞の浸潤所見（Fig. 2）を認め，giant and spindle cell carcinoma of urinary bladder, G3, pT3b, N1, v1 の診断であった．癌部の抗 G-CSF モノクローナル抗体による免疫組織化学染色（Fig. 3）では，腫瘍細胞の細胞質における G-CSF 蛋白発現が観察された．病理学的に，右壁内尿管までの浸潤像および 1 個の右外腸骨リンパ節転移所見が認められた．

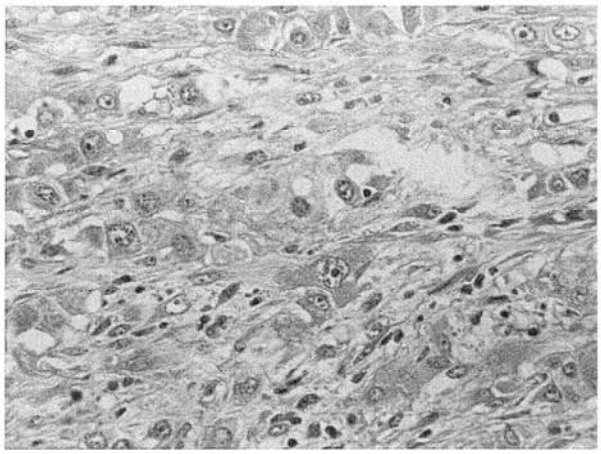

Fig. 2. HE staining (×400) showed giant and spindle cell carcinoma.

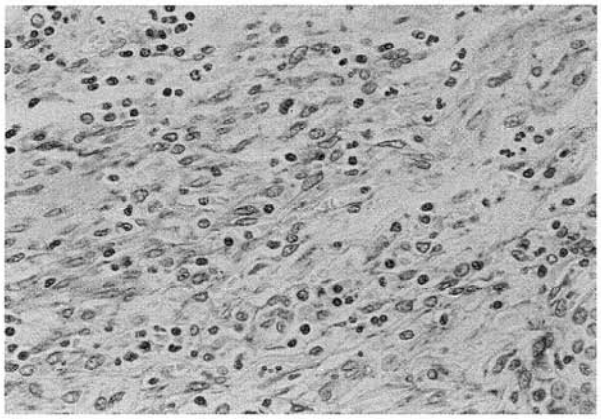

Fig. 3. Immunohistochemical staining (×400) with anti-granulocyte-colony stimulating factor (G-CSF) indicating the distribution of cancer cells expressing G-CSF.

術後経過は良好で手術 1 カ月後の血中 G-CSF 値は 84 pg/ml と軽度低下していた．2007年 1 月より術後補助化学療法として M-VAC 療法（MTX : 30 mg/m^2, VBL : 3 mg/m^2, DXR : 30 mg/m^2, CDDP : 70 mg/m^2）を 3 サイクル施行した．効果判定の画像検査所見では，多発性肺転移，肺門部および骨盤内リンパ節転移の新たな出現を認めた．さらに血清 G-CSF 値は 104 pg/ml までの再上昇を観察し，RECIST に基づく総合奏効度は PD であった．新規抗癌剤による化学療法の希望はなく，その後 UFT 内服での外来通院治療を行っていた．腫瘍進行に伴い徐々に全身状態が低下し，同年 5 月には 100,000/mm^3 までの白血球増多が観察された（Fig. 4）．最終的に術後 6 カ月目の2007年 6 月に永眠された．

考　　察

G-CSF 産生腫瘍とは，granulocyte-colony stimulating factor（G-CSF）などサイトカインを産生し，白血球増多を惹起する腫瘍である．Katoh らは腫瘍組

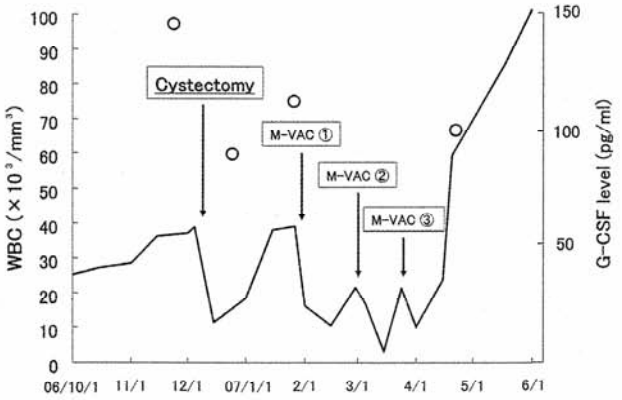

Fig. 4. Changes of WBC and serum G-CSF levels during the clinical course.

織中に G-CSF 遺伝子の転写産物を証明し，また，血中 G-CSF 活性が著しく上昇していたことより，悪性腫瘍に伴う白血球数増多を担癌による宿主反応ではなく，腫瘍による自律的かつ過剰なG-CSF産生によるものと報告した[1]．G-CSF 産生腫瘍の現在の診断基準としては，1）成熟好中球を主体とした著明な白血球数増加，2）血中 G-CSF 値の上昇，3）腫瘍切除や治療による 1，2）の改善，4）免疫組織化学染色による G-CSF 蛋白発現の確認の 4 項目が挙げられている[2,3]．自験例では明確な感染所見を随伴しない末梢血白血球数増多および癌部での G-CSF 蛋白発現が確認され，上記 1～4）の基準を満たすため，G-CSF 産生膀胱癌の診断に至った．

本邦におけるG-CSF産生膀胱癌に関しては，清水ら[4]の報告での未記載症例およびそれ以降の報告例が自験例を含めて，調べえたかぎりで21例認められている（Table 1）．よって，本邦では Itoら[5]の第 1 例目の報告以降，自験例を含め64例（会議録含む）が報告さ

Table 1. Twenty-one cases of bladder cancer producing G-CSF in Japan

No.	報告者	報告年	年齢	性別	主訴	診断	最高白血球数 (/μl)	血中 G-CSF 値 (pg/ml)	治療	予後
44	丸山	2002	46	F	肉眼的血尿	TCC ＞ AC, G3, pT1b 以上	40,100	82	Chemo, TC	術後 9 カ月生存
45	Hirasawa	2002	51	M	肉眼的血尿, 発熱	TCC＞SCC, G3	30,200	98.3	Chemo, TC	術後40カ月生存
46	石田	2004	75	M	肉眼的血尿, 発熱	SCC＞TCC, pT4N1	33,200	126	TC	術後 2 カ月で癌死
47	山本	2004	75	M	記載なし	TCC, G2, pT2a	記載なし	記載なし	TC	術後 4 カ月で癌死
48	山本	2004	48	M	記載なし	TCC, G3, pT2 以上	記載なし	記載なし	Chemo	癌死（8 カ月）
49	亀井	2004	67	F	頻尿，排尿時痛	TCC, G3, pT1bN0	34,390	1,320	Chemo, TC, RT	術後10カ月で癌死
50	北原	2004	75	M	排尿時痛	TCC, G3	26,000	190	施行せず	癌死（3 カ月）
51	Kitayama	2004	62	M	記載なし	TC 後の再発	180,000	296	施行せず	癌死（肺転移出現後 4 カ月）
52	片岡	2005	56	M	頻尿	TCC, G3	31,300	142	RT, Chemo	生存
53	阿部	2005	82	M	労作時息切れ	TC 後の再発，肉腫様癌＋TCC	90,790	396	再発腫瘍摘出	生存
54	石田	2005	78	M	排尿時痛	肉腫様癌＋TCC, G3，pT1	24,900	記載なし	TC	術後 5 カ月生存
55	木藤	2005	81	M	肉眼的血尿	UC, G3＞2	13,100	593	Chemo	癌死（3 カ月）
56	高木	2005	51	M	肉眼的血尿	TCC, G3, pT3bN1	44,500	198	TC	術後1.5カ月で癌死
57	塚	2005	66	M	排尿時痛	未分化癌，pT2aN0	53,000	268	TC	術後 4 カ月生存
58	吉野	2005	57	F	肉眼的血尿	TCC, G3	54,100	172	TC, RT	術後 2 カ月で再発，4 カ月で癌死
59	益田	2006	64	M	肉眼的血尿	UC, G3, pT2b	記載なし	記載なし	TC, Chemo	術後 4 カ月で癌死
60	喜多	2006	54	F	腰背部痛	紡錘形細胞肉腫	81,500	211	Chemo	生存
61	小松	2007	83	F	肉眼的血尿	TCC＋肉腫様癌, G3，pT1b	83,100	420	TUR-Bt	術後 2 カ月で癌死
62	中神	2007	83	M	肉眼的血尿, 排尿時痛	未分化癌，pT3b	46,600	119	TC	死亡
63	川島	2008	68	M	肉眼的血尿	UC, pT3a, G2＞3	89,100	153	Chemo, TC	術後 5 カ月で癌死
64	自験例	2008	56	M	肉眼的血尿	未分化癌，pT3b	100,000	145	TC, Chemo	術後 6 カ月で癌死

TCC : transitional cell carcinoma, UC : urothelial carcinoma, SCC : squamous cell carcinoma, AC : adenocarcinoma, TC : total cystectomy, RT : radiation therapy, Chemo : chemotherapy.

れており，これらについて臨床的検討を行った．

性差に関しては，2.2：1で男性が多かった．発症年齢の平均は67.9（46～94）歳であり，一般的な膀胱腫瘍と大きな差はなかった．男女別発症年齢の平均はいずれも68歳であり，性差による違いはみられなかった．

臨床症状は記載されていた52例中32例（62%）が肉眼的血尿，12例（23%）が排尿時痛や頻尿などの下部尿路症状であった．有症状症例が大部分を占めており，ある程度進行した状態で診断されていることが予想され，予後を不良にしている因子と考えられた．

最高の末梢血白血球数は13,100～476,000/mm^3（平均 69,900/mm^3，中央値 49,500/mm^3）で，血中 G-CSF 値は 52～7,360 pg/ml（平均 496 pg/ml，中央値 190 pg/ml）であり，いずれの報告においても高値を示していた．自験例を含めた本邦報告例において末梢血白血球数および血中 G-CSF 値の推移は病勢や治療効果を比較的よく反映しており，これらのモニタリングに非常に有用と考えられた．

組織型は移行上皮癌が37例，未分化癌が6例，扁平上皮癌が6例，移行上皮癌および扁平上皮癌の両成分を含むものが3例，肉腫様癌が3例，肉腫様癌と移行上皮癌の合併例が4例，腺癌と移行上皮癌の合併例が1例であった．通常の膀胱腫瘍の組織型に比較し，移行上皮癌の占める割合が低く，未分化癌および扁平上皮癌の割合が高い．また，grade の記載があった移行上皮癌43例中40例（93%）が G3 であった．未分化癌および低分化癌の割合が高く，これらの病理組織学的特徴が本疾患の予後不良に関与している可能性が示唆された．

治療に関しては，何らかの治療を行った53例中30例（57%）で膀胱全摘除術単独が施行されており，Ito ら[6]のように TUR-Bt のみで以後の再発，転移が認められなかったとする報告は1例のみであった．その他，膀胱全摘および化学療法が5例，膀胱全摘および放射線が1例，化学療法単独と放射線療法単独がそれぞれ4例と1例，化学療法および放射線が6例，腫瘍切除と TUR-Bt が各々2例であった．

予後については64例中44例（68.7%）で報告時すでに癌死を認め，そのほか他因死が1例，生存は17例，不明2例であった．膀胱全摘除術の施行症例でもその大部分は少なくとも5カ月以内に再発し，癌死に至っている．初診から死亡までの期間は平均5.7カ月，中央値5カ月であった．自験例も初診より10カ月で癌死に至っておりきわめて予後不良であった．

このように不良な予後を有する G-CSF 産生膀胱癌でも術後40カ月で再発を認めていない症例[7]もある．報告時の生存症例17例を検討したところ，男性11例，女性6例の内訳で平均年齢は64.9（46～83）歳であった．末梢血白血球数および血中 G-CSF 値は各々 20,010～132,500/mm^3（平均 43,441）および 73～1,320 pg/ml（平均283.4）であり，報告時の死亡例に比較し，いずれも有意に低値であり，さらにほぼ全例において治療後の白血球数および血中 G-CSF 値の基準値範囲内への改善が認められる．生存症例の検討結果より本疾患においては治療前の末梢血白血球数および血中 G-CSF 値が比較的低値であること，さらに治療後のそれらの数値の正常化が予後良好を予見する因子として重要と考えられた．最近，膀胱腫瘍細胞株において autocrine G-CSF/G-CSF receptor により促進される腫瘍細胞の浸潤能は β_1-integrin を介した系に依存するという報告[8]があり，上述の病理組織学的特徴だけでなく，このような分子生物学的特徴も本疾患の予後を不良にしている可能性が示唆された．この pathway は本疾患に対する新たな治療標的として興味深く，今後 *in vivo* への応用が期待される．

結　　語

G-CSF 産生膀胱癌の1例を経験したので，若干の文献的考察を加え報告した．

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