TABLE 3. POSTOPERATIVE COMPLICATIONS

	Clavien classification grade (%)[a]							
Procedure (No.)	*I*	*II*	*IIIa*	*IIIb*	*IVa*	*IVb*	*V*	*Totals*
Radical prostatectomy (277)	9 (3.2)	12 (4.3)	17 (6.1)	0 (0)	0 (0)	0 (0)	0 (0)	38 (13.7)
RPLND (3)	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33.3)
Donor nephrectomy (13)	1 (7.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.7)
Partial nephrectomy (74)	3 (4.0)	1 (1.3)	4 (5.4)	1 (1.3)	0 (0)	0 (0)	1 (1.3)	10 (13.5)
Radical nephrectomy (158)	8 (5.0)	10 (6.3)	0 (0)	1 (0.6)	0 (0)	0 (0)	0 (0)	19 (12.0)
Pyeloplasty (55)	0 (0)	2 (3.6)	1 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)	3 (5.4)
Nephrouretrectomy (97)	8 (8.2)	10 (10.3)	0 (0)	0 (0)	1 (1.0)	0 (0)	0 (0)	19 (19.6)
Simple nephrectomy (benign) (54)	2 (3.7)	1 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (5.5)
Adrenalectomy (128)	4 (3.1)	6 (4.7)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	11 (8.6)
Others (158)	2 (1.2)	2 (1.2)	1 (0.6)	0 (0)	1 (0.6)	0 (0)	0 (0)	6 (3.8)
Overall (1017)	37 (3.6)	45 (4.4)	23 (2.3)	3 (0.3)	2 (0.2)	0 (0)	1 (0.1)	111 (10.9)

[a]See Appendix 1.
RPLND = retroperitoneal lymph node dissection.

Postoperative complications classified according to the modified Clavien classification system are shown in Table 3. Grade I complications were recorded in 3.6%, grade II in 4.4%, grade IIIa in 2.3%, grade IIIb in 0.3%, grade IVa in 0.2%, grade IVb in 0%, and grade V in 0.1% of patients. Clavien grades I and II accounted for 73.8% of all postoperative complications. Complications of grade III or higher included 16 cases of urinary retention after a radical prostatectomy that were managed by Foley catheter placement using a flexible cystoscope, and 3 cases of indwelling ureteral stent for urinary leakage after a partial nephrectomy.

Intraoperative complications classified using the Satava classification are shown in Table 4. In 28 (73.7%) cases, intraoperative complications were grade II. The grade III complications were one air embolus, one pleural injury, three tumor injuries, and one rectal injury after a radical prostatectomy, which was diagnosed postoperatively because of an urethrorectal fistula and was managed by total parenteral nutrition.

The complication rates for the easy, difficult, and very difficult groups were 0% (0/57), 13.2% (71/536), and 12.8% (47/367), respectively (Table 5). The complication rate of the easy group was significantly lower than those of the difficult and very difficult groups. The complication rates of the difficult group and very difficult group, however, were not significantly different. Among procedures included in the difficult group, the complication rate of nephrouretectomy was significantly higher than that of other procedures of the difficult group ($P < 0.05$) (Table 6).

The complication rates in the first and last 300 cases were 8.6% and 17.6%, respectively ($P = 0.001$) (Fig. 1A). The percentage of procedures of the difficult and very difficult groups in the first and last 300 cases, however, was significantly higher in the latter period ($P < 0.001$) (Fig. 1B). The procedures

TABLE 4. INTRAOPERATIVE COMPLICATIONS

	Satava classification (%)[a]			
Procedure (No.)	*I*	*II*	*III*	*Totals*
Radical prostatectomy (277)	Arrhythmia: 2 (0.7)	Rectal injury: 3 (1.1)	Rectal injury: 1 (0.3)	6 (2.1)
RPLND (3)	0 (0)	0 (0)	0 (0)	0 (0)
Donor nephrectomy (13)	0 (0)	0 (0)	0 (0)	0 (0)
Partial nephrectomy (74)	0 (0)	0 (0)	Air embolus: 1 (1.3)	1 (1.3)
Radical nephrectomy (158)	0 (0)	Vascular injury: 2 (1.2) Splenic injury: 4 (2.5)	Tumor injury: 1 (0.6)	7 (4.4)
Pyeloplasty (55)	0 (0)	0 (0)	Pleural injury: 1 (1.8)	1 (1.8)
Nephrouretrectomy (97)	0 (0)	Vascular injury: 3 (3.1) Renal pelvis injury: 1 (1.0)	0 (0)	4 (4.1)
Simple nephrectomy (benign) (54)	0 (0)	Vascular injury: 3 (5.5)	0 (0)	3 (5.5)
Adrenalectomy (128)	Arrhythmia: 1 (0.8)	Liver injury: 3 (2.3) Gallbladder injury: 1 (0.8) Splenic injury: 1 (0.8) Intestine injury: 1 (0.8)	Tumor injury: 2 (1.5)	9 (7.0)
Others (158)	0 (0)	Vascular injury: 3 (1.9) Bladder injury: 2 (1.2) Nerve injury: 1 (0.6)	0 (0)	6 (3.8)
Overall (1017)	3 (0.3)	28 (2.7)	6 (0.6)	37 (3.6)

[a]See Appendix 2.
RPLND = retroperitoneal lymph node dissection.

TABLE 5. COMPLICATIONS IN PROCEDURES CLASSIFIED IN THREE GROUPS BY TECHNICAL DIFFICULTY USING THE EUROPEAN SCORING SYSTEM

Group	No. of cases	No. of patients with complications (%)*	No. of complications by classification (%)		
			Intraop	Postop	Total*
Easy	57	0 (0)	0 (0)	0 (0)	0 (0)
Difficult	536	71 (13.2)	28 (5.2)	59 (11.0)	87 (16.2)
Very difficult	367	47 (12.8)	7 (1.9)	50 (13.6)	57 (15.5)

*$P < 0.05$ Chi-square test: Between "easy" and "difficult", "easy" and "very difficult" is significant difference.

designated as difficult or very difficult increased annually (Fig. 2A). On comparing the eras of 1991 to 1999 *vs* 2000 to 2008, the difficult and very difficult procedures increased from 56.6% to 93.5% ($P < 0.001$) (Fig. 2B).

Discussion

Since laparoscopic surgery was introduced to the field of urology in the early 1990s, various complications have been reported. In the present retrospective study, we report a total complication rate of 14.6% and a fatality rate of 0.09%. In 1994, Parra and coworkers[9] reported a total complication rate of 15.2% and no mortality in 217 laparoscopic urologic surgical procedures. In the latest report by Fahlenkamp and associates,[10] the total complication rate in 2407 laparoscopic urologic procedures was 4.4% with a mortality rate of 0.08%, which is comparable to the results for a large series of laparoscopic cholecystectomies with complication rates between 2.5% and 5.0% and a mortality rate of 0.1%. Furthermore, Soulie and colleagues[11] reported a total complication rate of 5.4% and a mortality rate of 0.3% in 350 laparoscopic urologic surgical procedures. The reported mortality rates have remained unchanged since laparoscopic surgery was introduced. It has been shown that the complication rate decreases as surgeons' experience increases.

Rassweiler and coworkers[8] reported a total complication rate of 14% and open conversion rate of 10% in the first 50 cases of 200 laparoscopic urologic surgical procedures. In the last 50 cases, however, the total complication rate was 2% with open conversion rate of 4% by the same surgeon. In the present study, the complication rate was significantly higher in the last 300 cases than in the first 300 cases. We think that the complications in the earlier years were because of a lack of experience and poor technique, whereas the complications in later years were because of technical difficulties of the procedure. The percentage of procedures of the difficult or very difficult groups in the last 300 cases was significantly higher than in the first 300 cases.

The open conversion rate has been reported as 0.5% to 7.0% in urologic laparoscopies.[8–13] Our open conversion rate was 1.9%. Bleeding caused by vessel injury in six cases and adhesion to the surrounding viscera caused in nine cases represented the major causes of conversion to open surgery in this study. Rassweiler and associates[8] reported that the conversion rate to open surgery was 7.5%, and that the causes were bleeding or hematoma, technical problems such as severe perinephritic adhesions, or renal trauma, complex anatomy, and obesity. There is no consensus on whether open conversions because of technical difficulty should be included as complications.

Permpongkosol and associates[14] simply reported the open conversion rate separate from the complication rate. They did not clarify, however, what percentage of the conversions were caused by intraoperative complications. In contrast, Colombo and colleagues[15] included open conversions as intraoperative complications. We did not include the 11 cases of open conversion because of technical difficulty into the complication rate in this study.

Air embolism is one of the most dangerous complications in laparoscopic surgeries. Several cases have been reported during donor nephrectomies in the literature.[16] Theoretically, an increase in abdominal pressure is translated to an increase in intravenous pressure, resulting in an avoidance of the air embolism even though a venous laceration occurred. Actually, it is recommended that the pneumoperitoneum pressure be raised to 25 mm Hg to slow venous bleeding.[17] The high solubility of CO_2 used in laparoscopic surgery also prevents air embolism. If the abdominal pressure is extremely high and the venous wall with a laceration is pulled up simultaneously, however, then a large amount of CO_2 will enter the vein, resulting in a gas embolism. The air embolism we experienced during the laparoscopic partial nephrectomy was caused by the direct injection of compressed air into the cut ends of the branches of the renal vein at the renal parenchymal defect. The intra-abdominal pressure, which was monitored and recorded by the insufflation machine, was less than 12 mm Hg during

TABLE 6. COMPLICATIONS IN PROCEDURES AMONG THE DIFFICULT GROUP

Group	No. of cases	No. of patients with complications (%)*	No. of complications by classification (%)		
			Intraop	Postop	Total*
Nephrouretrectomy	97	21 (21.6)	4 (4.1)	19 (19.6)	23 (23.7)
Difficult group excludung nephroureterectomy	439	50 (11.3)	24 (5.4)	40 (9.1)	64 (14.5)

*$P < 0.05$ Chi-square test.

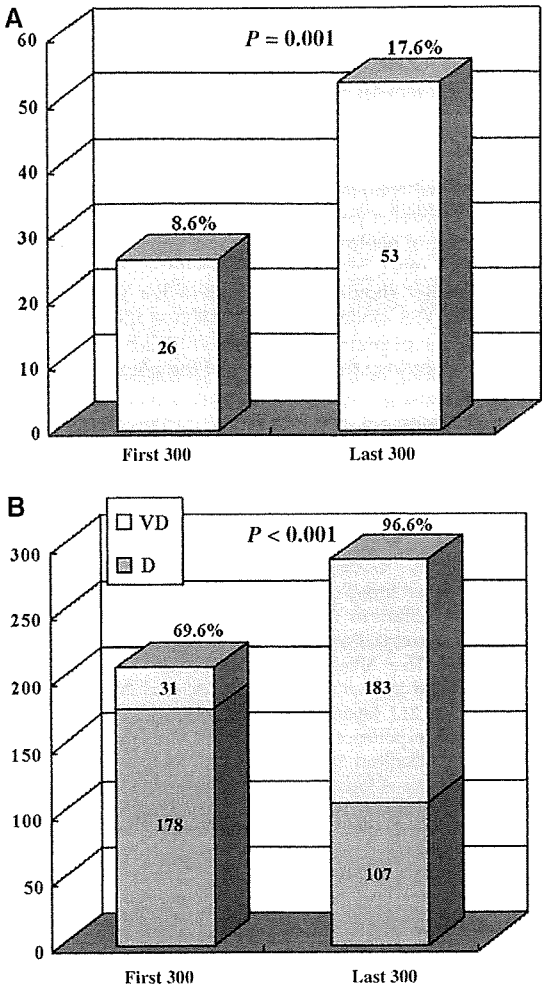

FIG. 1. (A) The percentage of complication in the first and last 300 cases. (B) The percentage of difficult (D) and very difficult (VD) groups in the first and last 300 cases.

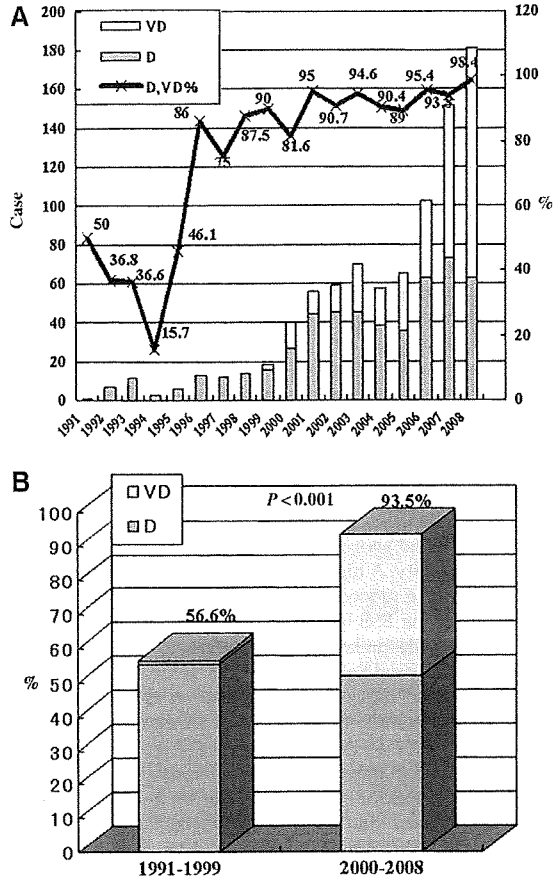

FIG. 2. (A) Yearly procedures of difficult (D) and very difficult (VD) groups. (B) Comparison of technical complexity of difficult (D) and very difficult (VD) groups for 1991 to 1999 *vs* 2000 to 2008.

the procedure, including the application of fibrin glue using compressed air. The external committee that reviewed the case concluded that the compressed air entered the vein directly through the venous openings at the parenchymal defect.

Air embolism caused by using an argon beam laser coagulator has been reported in cases of laparoscopic partial splenectomies[18] and open liver biopsies.[19] In those cases, it is hypothesized that the direct injection of gas into the cut ends of the veins resulted in gas embolism. Furthermore, Sezeur and coworkers[18] reported that the principal component of a pneumoperitoneum was not soluble CO_2 but insoluble argon after the use of an argon coagulator with trocars opened, resulting in a high risk of gas embolism. From our experience, it is preferable not to use compressed air or an argon beam coagulator on the parenchymal defects of a partial nephrectomy to prevent air embolism.

At present, there is no standardized classification system for urologic laparoscopic procedures according to technical difficulty. In 1999, Fahlenkamp and associates[10] classified urologic procedures according to technical difficulty as easy (diagnosis of and treatment of cryptorchidism, varicocelectomy), difficult (renal cyst resection, lymphocele fenestration, pelvic lymph node dissection, nephropexy, ureteral procedures), and very difficult (nephrectomy, adrenalectomy, retroperitoneal lymph node dissection) and compared the frequency of complications. The complication rates for easy, difficult, and very difficult procedures were 1.0%, 3.9%, and 9.2%, respectively. The complication rate for very difficult procedures was significantly higher than for the other procedures.

We classified the procedures into three groups according to the ESS for laparoscopic urologic surgery, which was proposed by Guillonneau and colleagues[5] in 2001. The ESS classification system is more detailed than other classification systems reported in the literature. Furthermore, experts in urologic laparoscopic surgery have validated this system based on their experience, and data from the international literature are supportive. In our study, the complication rates

in the difficult and very difficult groups were not significantly different.

If nephroureterectomy is included in the very difficult group, the complication rate of the very difficult group would be 17.6% and the difficult group would be 14.5%. The difference between these two groups would still not be statistically different. The very difficult group, however, would show a higher complication rate than the difficult group. Among procedures included in the difficult group, the complication rate of nephrouretectomy was significantly higher than that of other procedures ($P < 0.05$). Nephrouretectomy could be classified in the very difficult group based on the complication rate. Meta-analysis of complications of laparoscopic renal surgery in 2006 showed that the complication rate for nephrouretectomy was 18.8%.[4] Permpongkosol and coworkers[14] have also reported that a complication rate (40.9%) for nephrouretectomy was higher than that of other laparoscopic procedures.

ESS is classified mainly on a subjective scoring of the technical demands, operative risk, and the attention necessary.[5] The complication rate is substantially related to the operative risk and should be one of the factors that affect the technical difficulty. A higher complication rate is also a factor in upgrading the procedure. Colombo and colleagues[15] recommend that the ESS be prospectively and externally validated before widespread implementation.

We also compared the operative time, estimated blood loss (EBL), and blood transfusion rate between radical nephrectomy and nephroureterectomy, which are classified into the difficult procedure according to the ESS. The average operative time, EBL, and transfusion rate in a radical nephrectomy and nephroureterectomy were 305 minutes and 432 minutes ($P < 0.001$), 174 mL and 355 mL ($P = 0.0012$), and 5.0% and 8.2% ($P = 0.308$), respectively. These findings also indicate that nephroureterectomy is more technically demanding than radical nephrectomy. We did not analyze operative time or EBL in this study; these factors are also useful to validate the system.

The modified Clavien classification system for complications has become more widely used recently. This system, however, defines only postoperative complications and cannot be used for intraoperative complications.[20,21] National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 are also used to evaluate postoperative complications. We used the modified Clavien classification system because it is a more detailed system than NCI-CTC version 2.0. We also used the Satava classification for intraoperative complications.[7,22]

We defined the major complications as Satava grade II or higher and Clavien grade III or higher. There is no consensus on how to classify major or minor complications. For example, Permpongkosol and coworkers[14] defined major complications as enough morbidity to necessitate significant additional treatment and at least 2 more days of hospitalization. Bachmann and associates[23] defined that a severe disadvantage for the donor, including conversion, reoperation, transfusion, or effects on graft function were major complications in donor nephrectomy. Donnez and associates[24] defined conversion to laparotomy, hemorrhage necessitating blood transfusion, or a second surgical procedure to perform adequate hemostasis and the repair of urinary tract injuries or bowel perforation as major complications.

Classification systems for intraoperative and postoperative complications are still not unified in the urologic field. Establishment of a classification system for complications in the urologic field is needed for uniform evaluation.

Conclusion

We reported complications in 1017 urologic laparoscopic surgical procedures performed at our institution. The complication rate of nephrouretectomy was significantly higher than that of other procedures in the difficult group. Nephrouretectomy should be classified in the very difficult group of the ESS. Understanding the degree of technical difficulty and the potential complications for each procedure is important to prevent the occurrence of complications.

Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Tadashi Matsuda, M.D., Ph.D.
Department of Urology
Kanasai Medical University in Japan
Hirakata Shinmachi 2 tyoume 3-1
Hirakata City, Osaka 573-1191
Japan

E-mail: matsudat@hirakata.kmu.ac.jp

Abbreviations Used

CT = computed tomography
ESS = European Scoring System
EBL = estimated blood loss
NCI-CTC = National Cancer Institute Common Toxicity Criteria

「SNRIによるpseudo-pheochromocytoma」を呈したMEN1型の一例

東京大学病院　腎臓・内分泌内科

三島　英換　矢嶋　由紀　岡本　剛明　高橋　克敏　高野　幸路
福本　誠二　藤田　敏郎

はじめに

うつ病の治療薬として使用されるセロトニン・ノルアドレナリン再取り込み阻害薬(serotonin-noradrenaline reuptake inhibitor、以下SNRI)は、シナプス末端でのノルアドレナリン取り込み阻害作用を持つため、副作用として血圧上昇や動悸が起こりうる[1]。今回、高血圧、頻脈の症状に加えて血中、尿中カテコラミン濃度が著明に上昇し、褐色細胞腫クリーゼ様のダイナミックな病態を呈した、「SNRIによる薬剤性pseudo-pheochromocytoma」と考えられる多発性内分泌腫症1型(MEN1型)患者の一例を経験したので報告する。

1．症　例

【症　例】64歳　女性

【主　訴】意識障害、発熱、動悸、発汗過多

【既往歴】MEN1型(*men1*遺伝子1256G欠損によるframeshift mutation)の診断。52歳、55歳時に膵ガストリノーマ、膵GHRH産生腫瘍に対して手術施行。54歳時に原発性副甲状腺機能亢進症に対して副甲状腺摘出術施行。膵ガストリノーマと原発性副甲状腺機能亢進症が残存しており、当科外来にて通院加療を行っていた。なお、本症例のこれまでの詳細な経過に関しては以前に仁科ら[2]により報告されている。

【現病歴】4か月前からうつ病の加療のため、当院精神科に通院し内服加療を行っていた。3か月前からミルナシプラン、アミトリプチリンの内服をしており、以後は内服薬の変更は行われていなかった。1週間前から、傾眠がちになり、2日前から食事摂取も不可能な状態に全身状態が悪化し、当日家で倒れているところを家族が発見し当院搬送となった。なお、処方されていた内服薬の休薬や大量内服はしていなかった。

【内服薬】ミルナシプラン(トレドミン®)100mg、アミトリプチリン(トリプタノール®)20mg、ニトラゼパム(ベンザリン®)5mg、オメプラール20mg、ミチグリニド15mg

【入院時現症】身長137cm、体重27kg、BMI 14.3kg/m^2、意識状態JCSI-3、呼応反応はできるが傾眠状態であった。血圧216/106mmHg(普段の外来血圧は110/60mmHg)、脈拍130回/分(整)、体温39.5℃と著明な高血圧、頻脈、発熱を認めた。発汗は著明であり、高度の脱水状態であった。神経学的所見としては、筋固縮、ミオクローヌスは認めず、明らかな深部腱反射の亢進も認めなかった。

【入院時検査所見】(Table. 1)

血漿ノルアドレナリン(NA)6456pg/ml、尿中ノルメタネフリン(NM)1.2mg/day、メタネフリン(MN)0.12mg/day、尿中NA 454mg/dayと血中、尿中のカテコラミンならびに代謝物の著明な上昇を認めた。CKは軽度高値であった。

Table. 1　入院時検査所見
NA: noradrenaline　AD: adrenaline
NM: normetanephrine　MN: metanephrine

WBC	7000	/μl	LDH	551	IU/l	TSH	0.77	μIU/ml
Hb	16.3	g/dl	GOT	54	IU/l	FT4	0.87	ng/dl
PLT	16.9	×10^4/μl	GPT	45	IU/l	CRP	0.02	mg/dl
Na	149	mEq/l	BUN	35.3	mg/dl	urine:	pro	(3+)
K	3.1	mEq/l	Cr	0.73	mg/dl		OB	(+)
Cl	101	mEq/l	UA	5.5	mg/dl		glu	(-)
cCa	10.3	mg/dl	CK	748	IU/l			
IP	3.8	mg/dl	glucose	187	mg/dl			

plasma			urine					
NA	6465	pg/ml	NM	1.2	mg/day	NA	454	mg/day
AD	298	pg/ml	MN	0.12	mg/day	AD	14.9	mg/day

【画像所見】

I123-MIBGシンチグラムでは異常集積を認めず。腹部造影CTでは副腎に特記すべき所見はなく、褐色細胞腫を疑わせる腫瘤像は認めなかった。

【入院後経過】

入院後は、高血圧、頻脈、脱水に対しては点滴補液、ジルチアゼムの持続静脈内投与で対応を行った。病態の原因として薬剤性の影響も考えミルナシプランの内服を入院当日から中止した。しかし、うつ病治療薬をすべて中断することはうつ症状の急な増悪が危惧されるためアミトリプチリンの内服は継続した。入院3日目には意識状態は清明な状態にまで改善し、高血圧、頻脈、体温も

日単位での速やかな改善を認めた。入院時高値を示していた、血中、尿中のカテコラミンも入院10日目には低下を認めた(Figure. 1)。入院14日目に行ったクロニジン負荷試験(アミトリプチリン3日間休薬後施行)では、負荷後の血漿NAの低下を認めた(Table. 2)。以後全身状態は改善し、退院時には血圧も降圧薬が不要になった。うつ病の症状はアミトリプチリンのみでコントロールされており、ミルナシプランの再投与は行わなかった。

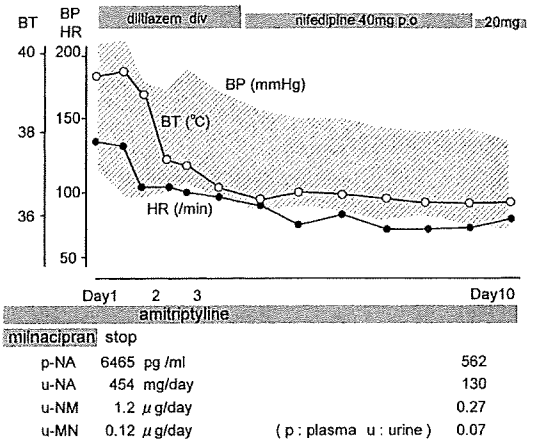

Figure. 1 臨床経過

Table. 2 クロニジン負荷試験

	負荷前		負荷3時間後
血漿NA	327	→	226pg/ml

2. 考 察

「pseudo-pheochromocytoma」とは、褐色細胞腫が存在しないにも関わらず褐色細胞腫で見られるような、高血圧・頻脈・多汗等の症状を呈する病態を指す。

本症例は、入院時に著明な高血圧・頻脈・多汗の症状に加え、血中・尿中のカテコラミンの著明な増加を認めたため、当初は病態の原因として褐色細胞腫クリーゼが疑われた。しかし、画像所見、クロニジン負荷の結果から、褐色細胞腫の存在は否定的であった。経過からは、三環系抗うつ薬であるアミトリプチリンの内服は継続したにもかかわらず、SNRIであるミルナシプランのみを内服中止して症状が速やかに改善したこと、内服中止後に血中NA、尿中MNの低下を認めたことから、本症例はSNRIに起因する「pseudo-pheochromocytoma」であった可能性が強く疑われる。

本症例におけるpseudo-pheochromocytomaの発生機序としては、SNRIのシナプス間隙でのNA取り込み阻害作用による、NA受容体に対する刺激増加に起因すると考えられる。NA受容体刺激増加により、血管収縮、心拍数増加が出現し、また脱水により薬物血中濃度が上昇、さらに薬物作用が増強するという悪循環を経て、病態が数日かけて完成したものと推測される(Figure. 2)。また、SNRIの作用に加えて、同じくシナプス末端でのNAの再取り込み阻害作用を持つ三環系抗うつ薬を内服していたこと、小柄な体格にも関わらずミルナシプランの投与用量が100mg/日と保険収載量の最大用量を内服していたことも病態の発生に寄与した要因と考えられる。既報の薬剤性pseudo-pheochromocytomaの症例も、すべてシナプス間隙のNA濃度を高める薬剤(SNRI、SSRI、MAO阻害薬、三環系抗うつ薬)を2種以上を併用していた例での報告である[3),4)]。

本症例と症状(発熱・頻脈・高血圧・意識障害)が共通しており、鑑別すべき病態としてセロトニン症候群と悪性症候群が挙げられる。セロトニン症候群とは、セロトニン作動薬内服時(特に併用時)に中枢神経系セロトニン機能の異常亢進が起こり中枢神経・自律神経症状を呈する症候群であり、近年SSRIでの報告が増えているが、SNRIでの報告例もある。

セロトニン症候群と本症例の病態を比較すると(Table. 3)、明らかな腱反射やミクローヌスを認めないこと、症状進展に数日かかったこと、症状改善が原因薬物中止から24時間以上かかったことが典型例と一致しない。セロトニン症候群の診断基準であるSternbach's criteria[5)]に合わせても、「症状出現が薬剤の増量や追加と一致している。」という項目が本病態ではあてはまらない。また、悪性症候群としては、筋固縮がない点、CPKが軽度高値に留まっている点、症状改善が悪性症候群としては早すぎる点から考えにくい。

SNRIは副作用の少なく、従来の抗うつ薬と比べて安全な薬剤と考えられているが、通常量の内服でも血圧の上昇が起こる例もあり[7)]、内服中は血圧、脈拍の変化にも注意を払う必要があると考えられる。また、うつ病治療に対してSNRIを含む抗うつ剤の多剤併用は、本症例のような重度の高血圧、頻脈を惹起する可能性も念頭に置くべきである。

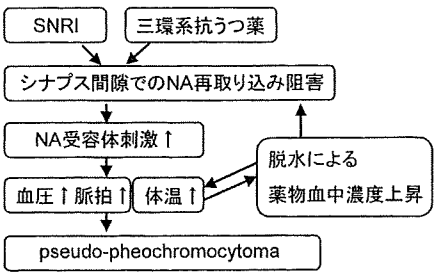

Figure. 2 病態仮説

Table. 3 本症例と鑑別疾患との病態比較 6)から引用改変

	本症例	セロトニン症候群	悪性症候群
共通症状	発熱・頻脈・高血圧・自律神経障害・意識変化		
原因薬物	SNRI	セロトニン作動薬	ドパミン拮抗薬
症状進展	数日	< 12時間	1~3日
原因薬物中止からの症状改善	約24時間	< 24時間	平均9日
筋・反射	筋固縮 (−) ミオクローヌス (−)	腱反射亢進 ミオクローヌス	筋固縮
血中・尿中カテコラミン	著明高値	(増加 ?)	

結 語

SNRI 内服中に、褐色細胞腫クリーゼ様の病態が生じた場合は、薬剤性の pseudo-pheochromocytoma を鑑別すべきであり、疑われる場合は、薬剤の中止を含めた適切な対処が必要である。

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^{131}I-MIBGによる内照射療法が奏効した悪性褐色細胞腫の一例

A Patient with Malignant Pheochromocytoma Showing Favorable Responses to ^{131}I-MIBG Therapy.

儀保　順子 Junko Gibo
有坂有紀子 Yukiko Arisaka
樋口　徹也 Tetsuya Higuchi
織内　昇 Noboru Oriuchi
遠藤　啓吾 Keigo Endo

【はじめに】

褐色細胞腫は副腎髄質や交感神経節などのクロム親和性細胞から発生する腫瘍であり、そのうち悪性褐色細胞腫は約10%程度と考えられている。この腫瘍はノルアドレナリンなどのカテコールアミンを産生・放出することが多く、その場合には特徴的な臨床症状を呈する。

治療としては手術が原則であり、腫瘍を全摘出できれば、症状は軽快する。手術不能例や多発転移ならびに術後再発例は、化学療法、放射線治療および内照射療法の対象となる。内照射療法は褐色細胞腫が^{131}I-MIBGを取り込む特徴を利用して、^{131}Iのβ線により治療効果を発揮する。

^{131}I-MIBGによる内照射療法が奏効した悪性褐色細胞腫の一例を報告する。

【症　例】

患者：30代、女性

主訴：発汗、高血圧

既往歴：

2004年7月、流産時に血圧が急上昇し近医を受診した。検査の結果、左副腎の褐色細胞腫と診断され同年11月に左副腎摘除術を施行した。術後に血圧は正常化した。2006年10月に血中ノルアドレナリンが高値となり血圧が再度上昇した。2007年6月の^{131}I-MIBGシンチグラフィにて異常集積を認め、悪性褐色細胞腫の転移と診断された。2007年8月の^{123}I-MIBGシンチグラフィでは、新たに両肩、両肺、右鼠径部にも異常集積を認めた。

【検査所見】

Hb：13.0 g/dl, WBC：7000 /μl, Plt: 27.5万 /μl

血中：アドレナリン≦0.01 μg/ml,

ノルアドレナリン：12.31 μg/ml,

ドーパミン：0.27 μg/ml

蓄尿：ノルアドレナリン：1640.4 μg/ml,

ドーパミン：1397.7 μg/ml

尿VMA:23.15 mg/ml

【診　断】

悪性褐色細胞腫の左副腎再発、多発性骨・リンパ節転移

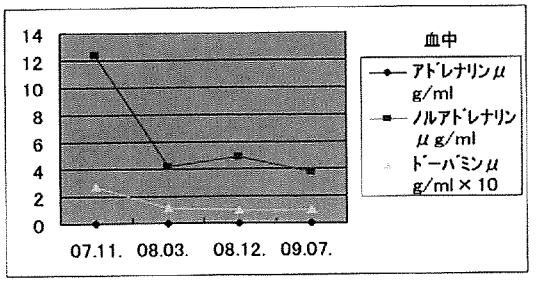
【治　療】

2007年12月～2009年4月まで、^{131}I-MIBG（200 mCi）を3回投与した。

【結果のまとめ】

自覚症状に関して発汗は2回目の治療後に改善した。血中及び尿中のカテコールアミンは徐々に改善した（図1、2）。^{123}I-MIBGシンチグラフィ及びFDG-PETでは、左副腎の再発巣など一部の病変に対しては著明な効果ではなかったが、肺内転移、骨転移、腹部リンパ節転移など大多数の転移巣への集積は徐々に低下し、3回の治療後にはほとんど集積を認めない病巣も見られた（図3、4、5）。

図1．治療前後の血液検査所見



群馬大学大学院医学系研究科　放射線診断核医学
Department of Diagnostic Radiology and Nuclear Medicine,
Gunma University Graduate School of Medicine

図2. 治療前後の尿中検査所見

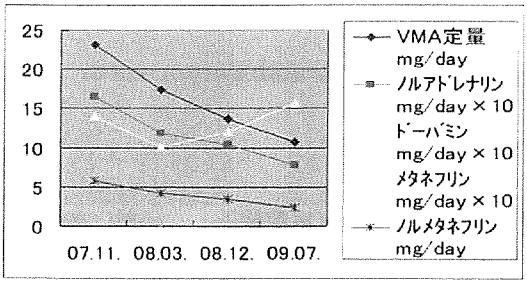


図3. 治療前後のMIBGシンチグラフィ所見

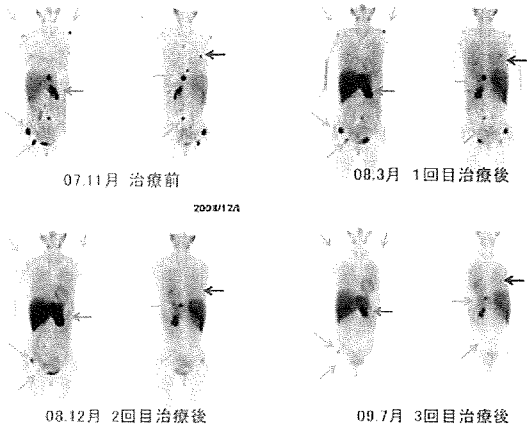
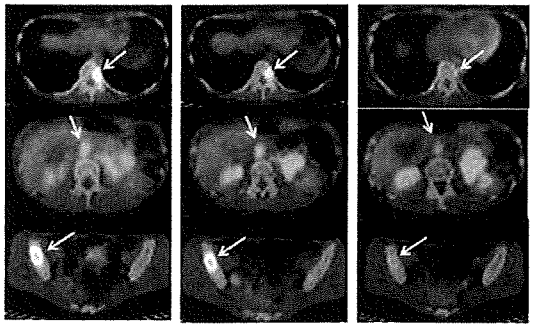


図4. 治療前後のFDG-PET/CT（横断像）所見
07年11月（治療前）08年3月（1回目治療後）08年12月（2回目治療後）



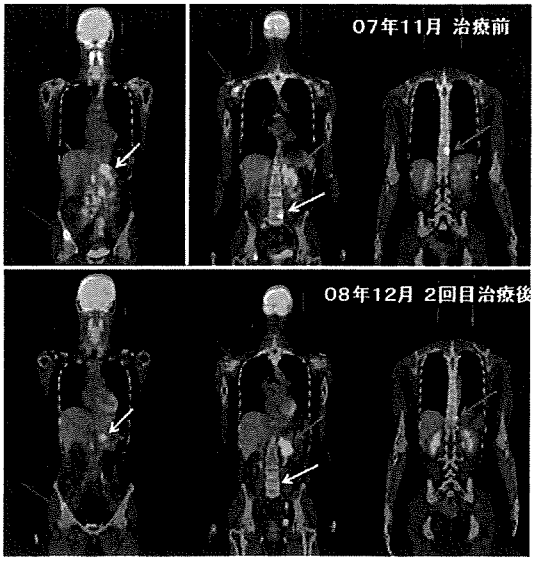
【考　察】

褐色細胞腫は副腎髄質や交感神経節から発生する腫瘍であり、その中で約10～20%程度が悪性褐色細胞腫である。褐色細胞腫は放射線ヨウ素を標識したノルエピネフリンの類似体であるmeta-iodobenzylguanidine (^{131}I-MIBG, ^{123}I-MIBG) が集積するため、病巣の検出ができる。MIBG内照射療法は1984年に最初の報告以来、手術不可能ないし悪性褐色細胞腫の治療として^{131}I-MIBGによるアイソトープ内照射療法が行なわれている[1]。多発性の転移を有する症例に対しては、有力な治療選択肢の一つである。わが国では保険適応でないため、個人輸入して使用されている。内照射治療を施行している施設は、現在のところ当院の他に北海道大学、金沢大学と鹿児島大学である[2,3]。

MIBG内照射療法は化学療法であるCVD (cyclophosphamide、vincristine、dacarbazine) 療法と較べると、治療効果は同程度であると報告されている[4,5]。内照射療法の治療奏効率は約30～50%と高くはないが、^{131}I-MIBGは腫瘍に特異的に集積するため、化学療法よりも全身の副作用が少ないことが利点である。副作用として、高血圧クリーゼ、悪心・嘔吐、骨髄抑制などがある。晩期の副作用としては、治療に際して甲状腺のブロックや唾液排泄の促進などを行ったとしても甲状腺機能低下症や唾液腺機能の低下などが見られることがある。今回の症例では目立った副作用がなく、発汗などの症状が改善し、血中・尿中カテコールアミンは約50%低下、画像上も集積低下があり、症状のコントロールとともに客観的な抗腫瘍効果も見られた。

^{131}I-MIBG治療により腫瘍が縮小する症例は少ないが、症状の緩和やデータの改善が半数以上の症例に認められるという報告がある。今回の症例のような多発転移および他の治療法の効果が乏しい症例に対しては、非常に期待できる治療法である。

図5. 治療前後のFDG-PET/CT（冠状断像）所見



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NOTE

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A Large Deletion in the Succinate Dehydrogenase B Gene (*SDHB*) in a Japanese Patient with Abdominal Paraganglioma and Concomitant Metastasis

HITOMI KODAMA[1], MASATOSHI IIHARA[1], SUMIKO NISSATO[2], KAZUMASA ISOBE[2], YASUSHI KAWAKAMI[2], TAKAHIRO OKAMOTO[1] AND KAZUHIRO TAKEKOSHI [2]

[1] *Departments of Endocrine Surgery, Tokyo Women's Medical University, Tokyo, Japan*
[2] *Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki, Japan*

Abstract. Recently, mutations in nuclear genes encoding two mitochondrial complex II subunit proteins, succinate dehydrogenase D (*SDHD*) and *SDHB*, have been found to be associated with the development of familial pheochromocytomas and paragangliomas (hereditary pheochromocytoma/paraganglioma syndrome: HPPS). Growing evidence suggests that the mutation of *SDHB* is highly associated with abdominal paraganglioma and the following distant metastasis (malignant paraganglioma). In the present study, we used multiplex ligation dependent probe amplification (MLPA) analysis to identify a large heterozygous *SDHB* gene deletion encompassing sequences corresponding to the promoter region, in addition to exon 1 and exon 2, in a malignant paraganglioma patient in whom previously characterized *SDHB* mutations were undetectable. This is the first Japanese case report of malignant paraganglioma, with a large *SDHB* deletion. Our present findings strongly support the notion that large deletions in the *SDHB* gene should be considered in patients lacking characterized *SDHB* mutations.

Key words: Malignant pheochromocytoma, *SDHB*, MLPA, HPPS (hereditary pheochromocytoma/paraganglioma syndrome), paraganglioma

THE NUCLEAR GENES encoding two mitochondrial complex II subunit proteins, succinate dehydrogenase D (*SDHD*) and *SDHB*, have been reported to be associated with the development of familial pheochromocytoma and paraganglioma (hereditary pheochromocytoma/paraganglioma syndrome: HPPS) [1, 2]. Growing evidence suggests that point mutations in *SDHB* are highly associated with abdominal paraganglioma and the following distant metastasis (malignant paraganglioma) [3-8]. Indeed, it has been found that *SDHB* mutations are present in 40% to 50% of malignant pheochromocytoma/paraganglioma patients which far exceeds the incidence of mutations of other genes in these malignant tumors. By contrast, among all patients with malignant pheochromocytoma/paraganglioma, the frequency of *SDHB* mutations is reported to be around one third, suggesting that *SDHB* mutations in these malignant tumors may not be as rare as expected [9].

It should be noted, however, that these findings are based on mutations including point mutations as well as small deletions, which are detectable by direct sequencing method [3-9]. Since large deletions are rare and are undetectable using this method, neither the frequency nor the clinical manifestation associated with large *SDHB* deletions is well known. Recently, in addition to these mutations, the use of methods such as multiplex ligation-dependent probe amplification (MLPA) and quantitative multiplex PCR of short fluorescent fragments (QMPSF) have resulted in increased reports of large *SDHB* deletions [10-18].

Here we report a large heterozygous *SDHB* gene deletion encompassing sequences corresponding to the promoter region, in addition to exon 1 and exon 2, in a malignant paraganglioma patient in whom previously characterized *SDHB* mutations were undetectable. This is the first Japanese case report of malignant

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Correspondence to: Kazuhiro TAKEKOSHI, M.D., Ph.D., 1-1-1 Tennoudai, Tsukuba, 305-8575, Japan.
E-mail: K-takemd@md.tsukuba.ac.jp

Table 1. Biochemical findings on the first admission.

	Plasma A	*Plasma NA*	*Urine (spot) MN*	*Urine(spot) NMN*
	pg/ml (≦30)	pg/ml (≦500)	ng/mg・cr (≦200)	ng/mg・cr (≦300)
1995/8/26	10	6000	485	10535
1995/10/19	10	400	236	509
2009/5/30	24	1654	10	1580

Plasma noradrenaline as well as urinary normetanephrine, as assessed by high-performance liquid chromatography (HPLC), were significantly elevated at first admission (August 1995).
A: adrenaline; NA: noradrenaline; MN: metanephrine; NMN: normetanephrine

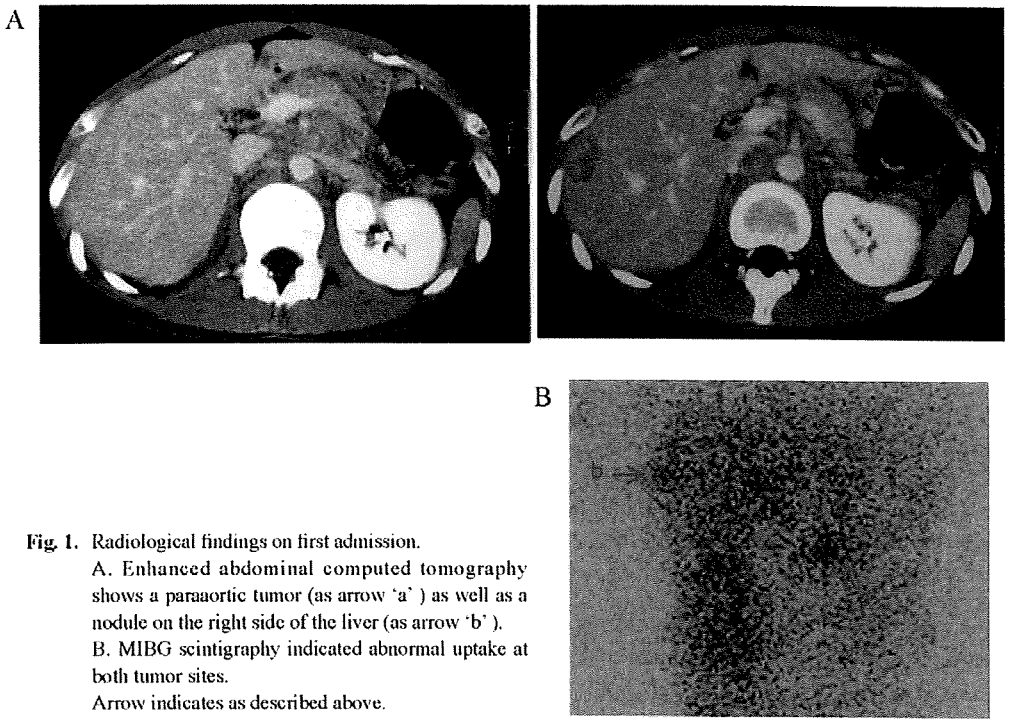

Fig. 1. Radiological findings on first admission.
A. Enhanced abdominal computed tomography shows a paraaortic tumor (as arrow 'a') as well as a nodule on the right side of the liver (as arrow 'b').
B. MIBG scintigraphy indicated abnormal uptake at both tumor sites.
Arrow indicates as described above.

paraganglioma with a large *SDHB* deletion.

Subjects and Methods

Patient

A 25 year-old Japanese female with a 2-year history of hypertension was referred to our hospital for treatment for abdominal and liver masses in July 1995. No familial incidence of pheochromocytoma or paraganglioma was known in her kindred.

On first admission in August 1995, the patient's catecholamine level was significantly elevated as shown in Table 1. Enhanced abdominal computed tomography (CT) revealed a paraaortic tumor and a metastatic nodule on the right side of the liver (Fig. 1A). MIBG scintigraphy indicated abnormal uptake at both tumor sites (Fig. 1B).

An operation was performed in September 1995,

but the main tumor was unresectable because of severe invasion. Extraadrenal malignant paraganglioma was diagnosed through pathological investigation. After surgery in October 1995, her catecholamine level was slightly elevated, but hypertension was diminished postoperatively with doxazosin (1-2 mg/day). This subject was followed up annually along with measuring plasma catecholamine as well as urinary metanephrine. In May 2009, 14 years after the first operation at age 39, multiple nodules in the left sided paraaorta were detected by abdominal CT. Consistent with these nodules, MIBG scintigraphy showed abnormal uptake and her catecholamine level was again increased. Therefore, recurrence or remnant of malignant paraganglioma was strongly suspected.

Given the well-documented association of mutations in the *SDHB* gene with malignant pheochromocytoma/paraganglioma, we decided to carry out germline analysis of the *SDHB* gene.

Genetic analysis

Subjects in this study were informed of the possibility of genetic study, its implications, and its purpose. Written informed consent was obtained from those wishing to participate in the study, and the study was approved by the ethics committee of the Medical Faculty of Tsukuba University, Tsukuba, Japan. Blood samples were collected from the participants and DNA extracted using a blood DNA extraction kit (Wako, Osaka, Japan).

PCR and sequence analysis

Peripheral blood for germline DNA analysis was drawn from the patient after written informed consent was obtained. Using blood DNA, the eight exons of the *SDHB* gene were screened with intronic primers [19-21]. PCR was carried out as described previously [19-21]

PCR amplicons were column purified and subjected to semi-automated sequencing using the above primers, dye terminator technology, and the Long-Read Tower DNA sequencer (Amersham Pharmacia Biotech) [19-21]

MLPA analysis [22]

We used a commercially available kit, SALSA MLPA P226 (MRC-Holland, Amsterdam, The Netherlands) according to the manufacturer's instructions. Multiplex ligation-dependent probe amplification (MLPA) is a semiquantitative method designed to detect deletions/duplications of one or more exons at the genomic level. The P226 kit includes nine specific probes for *SDHB*, six for *SDHC*, and five for *SDHD* to be used in one single reaction.

Results

SDHB mutation analysis

Mutations in the eight exons of the *SDHB* gene in the subject's germline DNA were undetectable by direct sequencing. While the majority of patients undergoing *SDHB* mutation analysis have missense and nonsense mutations, some mutation negative patients have been reported to carry either large partial or total deletions of the *SDHB* gene [10-18]. To investigate this possibility, we carried out MLPA and identified a heterozygous *SDHB* gene deletion encompassing sequences corresponding to the promoter region, exon 1 and exon 2 (Fig. 2A, B).

Discussion

Current evidence suggests that mutations in *SDHB* are frequently associated with abdominal paraganglioma and the following distant metastasis [3-9]. Therefore, it is recommended that all patients with metastatic disease, especially from paraganglioma, be tested for *SDHB* mutations. It should be noted, however, that these findings are largely based on mutations which are detectable by direct sequencing [3-9].

While many *SDHB* mutation such as missense/nonsense mutations have been identified, some cases with large deletions have been described (Fig. 2B) [10-15].

The precise frequency of *SDHB* deletion across all *SDHB* positive cases remains to be established. Two occurred in exon 1 of *SDHB*, including one of approximately 20 kb, previously demonstrated by Cascon *et al.* [12]. Consequently, the frequency of *SDHB* deletion across all French *SDHB* positive cases was estimated at 8.3% (8/96).

In a large cohort of Spanish patients, seven independent families were found to carry deletion in the *SDHB* gene, representing 28% of positive *SDHB* cases [17]. The presence of founder mutations in the Spanish population could also explain the high rate of *SDHB* mutations in this series. Taken together these recent results indicate that large *SDHB* deletions represent approximately 10% of all *SDHB* mutations and sug-

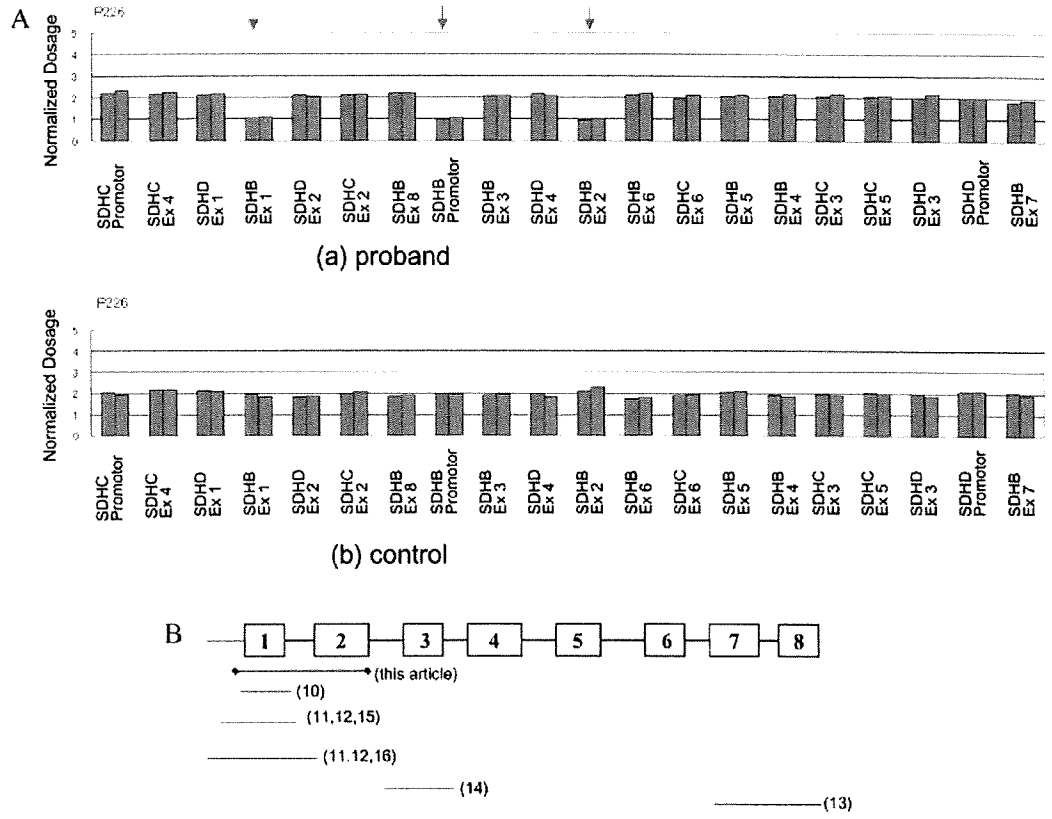

Fig. 2. MLPA analysis.

A. Normalized probe intensities for (a) the subject (proband) with the SDHB gene deletion and (b) a control subject without the deletion are shown.

B. In the proband, MLPA identified a heterozygous deletion of the SDHB promoter, exon 1 and exon 2, changing the normalized dosage to half that of the control subject, as indicated by arrows.

C. Eight exons of SDHB are represented diagrammatically. The bar below indicates the approximate location of large deletions. Note that these bars do not reflect exact lengths of large deletions.

gest to us that these tests capable of detecting such large deletions, such as MLPA, should be made routine. Conceivably, MLPA could be used to screen for large deletions in all three *SDHx* genes in a single test.

In contrast to the frequency estimated in the studies described above, MPLA analysis of a large cohort of Italian patients detected no large genomic *SDHB* deletions (only two cases of large deletion of *SDHD* were found in this series, such that *SDHB*=0/24 and *SDHD*=2/47) [18]. Based on these results the authors suggested that MLPA would not be worthwhile on a routine basis [18]. However, these different results might depend not only on the geographic origin of the series but also on the criteria of patient selection and classification. For example, the French cohort included only paraganglioma patients, and excluded a single pheochromocytoma (adrenal catecholamine secreting tumor) patient. In the present study, we have carried out MLPA analysis in five malignant cases (initial location of tumor, four: extra-adrenal, one: adrenal), in which point mutations in the *SDHB* gene were undetectable. A large deletion in the *SDHB* gene was detectable in only one patient (the case presented here), corresponding to a deletion frequency of 20% (1/5), in agreement with previous studies [16, 17].

Given that only a small number of *SDHB* deletion cases have been described [10-18], it is difficult to meaningfully compare the phenotypes and pene-

trance of patients with either point mutations or large deletions in *SDHB*. The combined findings described above, however, indicate that they share almost similar phenotype as well as penetrance. Indeed, in a previous study of 82 *SDHB* point mutation carriers, an estimated 45% developed paraganglioma by age 40 [7]. In a recent report, with a smaller number of subjects in large family (23/41), the penetrance of paraganglioma related to exon 1 large *SDHB* deletion based on a Kaplan-Meier analysis was slightly lower and estimated to be 35% by age 40 [16].

In conclusion, we have identified a large *SDHB* gene deletion, which includes the promoter region, in a patient with abdominal paraganglioma concomitant with distant metastasis. This is the first Japanese case report of its type and our findings strongly support the notion that large deletions in *SDHB* should be considered in patients in which mutations of *SDHB* genes are undetectable.

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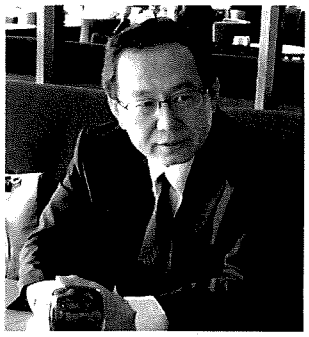
論　壇

難病（褐色細胞腫）治療の現状と将来展望



独立行政法人 国立病院機構
京都医療センター　臨床研究センター
内分泌代謝高血圧研究部　部長
成瀬 光栄

昨年から調査・研究の対象が大幅に追加された難病

診断と治療が困難な病気は一般に‘難病’と呼ばれます。厚生労働省ではその中でも特に、1）頻度が少なく（おおよそ総数5万人以下）、2）原因が不明で、3）有効な治療法がなく、4）患者の生活面での影響が大きい疾患を難治性疾患克服研究事業の調査研究対象として‘特定疾患’と呼んでいます。そしてその中から特に治療が困難で医療費も高額な疾患は、医療の確立・普及、患者の医療費負担軽減を目的として特定疾患治療研究事業の対象として医療費の助成制度を設けています。難治性疾患克服研究事業の対象疾患は123疾患、特定疾患治療研究事業の対象は45疾患です。‘難病’は何らかの行政的な取り組みがないとその診断・治療法の進歩は期待できません。しかし、特定疾患、特に医療費の助成対象を無制限に増やすと、莫大な医療費になることが予想されます。このような背景もありこの10年間はほとんど新しい特定疾患は増加しませんでしたが、平成19年8月に枡添要一氏が厚生労働大臣に就任後、C型肝炎に対する社会的関心の高まりとも密接に関連して、難病対策が大きく方針転換した。即ち、難病を放置しておくことは患者さんのQOL、予後を悪化させるのみでなく、結局は医療費の増加につながるとの総合的観点から難病対策強化の必要性が認識されたといえます。平成20年に特定疾患が7疾患追加され130に増加しました。更にこれまで対策が十分でなかったその他の様々な難病も注目され、平成21年4月には新たに25疾患が調査奨励研究の対象として決定されました。その内の一つが内分泌の病気の褐色細胞腫です。

転移して初めて悪性腫瘍と分かる厄介な病気、褐色細胞腫

身体の中の様々な部位の内分泌に病気ができます。腎臓の上に副腎がありますが、そこにできる腫瘍の一つが褐色細胞腫です。副腎腫瘍からカテコールアミンというホルモンを出し、高血圧を呈する病気で、腫瘍が見つかれば手術でとってしまえば治ります。昔はホルモン測定が難しく、副腎の病気を検査する画像検査も良いものがなかったので、診断が難しかったのですが、CTやMRIなどの進歩が著しく、診断が容易になりました。

診断が容易になったことで、一旦は‘特に難しい’病気ではないと思われがちになりましたが、この10年ほどをみていますと、治ったはずの患者の方の2割くらいの方が数年後、早い方では1年ぐらい、長い方では30年という期間で、色々な所に転移を示す例があることが分かったのです。手術して完治したと思い普通に生活していたら、あるとき突然転移していることが分かります。良性だと思っていたら何年か経てから悪性のものだと分かるという、とても厄介な疾患といえます。転移が見つかった際には手術、化学療法や放射線治療が行われますが、確実に有効なものはなく、次第に悪くなっていきます。20代、30代前半の若い方にも多く、子どもさんも小さいので、精神面でも経済面でも非常に大きな負担となります。

もう一つ大変難しいことは、普通は最初の手術時で組織をとれば良性か悪性かが分かるのですが、この病気はそれが分からないところが厄介なのです。病理組織の専門家がいくら顕微鏡で観察しても、細胞の形などからでは良性か悪性かが確実には分かりません。明らかに悪性

でなければ良性ということになり、転移して初めて悪性のものと分かる厄介な病気なのです。全国各地に患者さんがおられますが、実情は明らかではなく、悪性と判明して治療に難渋し大学病院に紹介されることが少なくありません。

私自身の専門は内分泌・高血圧の分野で、特にレニン・アンジオテンシン・アルドステロン系、副腎皮質疾患が専門ですので、特に褐色細胞腫を専門とするわけではありませんが、実際の診療面では転移して治療法に困っている患者さんを診察することが少なくなく、なんとか対策を講じる必要があると感じてきました。わが国では褐色細胞腫を特に専門として診療、研究している先生は極めて少ないのが現状で、病気としての注目度は低いといえます。そこで、診療の分野で少しでも関連のある診療科（診断に関わる内科、放射線科、治療に関わる放射線科・核医学科、手術に携わる泌尿器科、外科、内分泌外科など）の先生方に声をかけ、私が所属する国立病院機構京都医療センターの内分泌代謝臨床研究センターの活動の一環として、ワーキンググループを立ち上げ活動を始めました。その後、日本内分泌学会から臨床重要課題として取り上げられ、学会としての検討委員会の活動が始まり、更に平成21年4月からは厚生労働省難治性疾患克服研究事業の調査奨励研究として取り上げられ、新たな研究班を組織しました。全国の約2,400の医療機関、約6,500の診療科を対象した調査を実施し、現在、一次調査を終了、より詳しい内容に関する二次調査を実施中です。

私たち医療関係者による厚労省研究班の活動と並行して、患者さん側の活動も活発となってきており、患者会「褐色細胞腫を考える会」が今年の2月に結成されました。若い方を含めていろいろな年齢層の方が参加されており、参加者も増えているとのことです。患者様は病気のための定期的な通院あるいは入退院を繰り返しているため、仕事と家庭生活で余裕のないところを、メンバーがお互いに協力しつつ定期的に会合を開いたり、厚労省に陳情に行ったり、ホームページの開設やニュースレターの発行など、大変な努力をされて活動されています。医療側・行政側の取り組みである厚労省の研究班と患者さん側の取り組みである患者会の両輪がようやく今年になって動き始めたわけで、私達が活動を始めて5年を経て漸く、褐色細胞腫・悪性褐色細胞腫に対する対策の大きな第一歩を踏み出したといえます。

きちんとした対策により、診療技術の向上と患者さんの予後、QOLの改善が可能と考えられますが、その第一歩が正確な実態調査による患者数の把握です。今のところ、患者さんは1,000人～1,500人、そのうち悪性はおそらく100人～200人くらいという中間データが出ています。正確な疫学調査結果は早期診断法や新たな治療薬の開発の基盤になるといえます。平成21年7月18日に研究班の第一回班会議を開催し、全国の大学の関連診療科の先生方が班員として参加されました。今後、全国調査に加えて各大学ごとの過去5年間の調査をしていただき、データを充実させる予定です。

高血圧の中に紛れ込んでいる褐色細胞腫

実地医家の先生は滅多に出会わない病気と思います。高血圧が発見の重要なきっかけとなります。一見、血圧が高いだけですから本態性高血圧と区別がつきませんが、高血圧の中に紛れ込んでいる可能性を常に考慮する必要があります。最近では80歳代にも見つかり、患者さんは全年齢層にいます。症状はさまざまで頭痛や動悸などがありますが、これらの症状は他のいろいろな病気で見られるので発見が難しいのです。この病気を疑って血液検査でカテコールアミンの測定、腹部エコーやCTなどの検査をして初めて発見できます。約8割は手術で完全に治ってしまう良性ですが、約2割が手術のあとどこかに残っていてそれが転移する悪性です。良性と悪性では予後の差が大きく、その区別がつきにくい難しい病気です。

世界では、米国のNIH（国立衛生研究所）が中心になり3年ほど前から疾患の解明のため積極的な取り組みを始めています。NIHが関わっていますので、米国内のみならずヨーロッパでも非常に関心が高まっており、米国内での患者会の活動や患者向けの情報提供も非常に進んでおり、わが国でも今後更に取り組みを強めていく必要があるといえます。

褐色細胞腫は良性と悪性の区別が困難で転移して初めて悪性であることがわかる病気で、しかも、悪性例の治療法が未確立です。今、正に難病である褐色細胞腫の疾患解明の新たなスタート地点に立ったといえます。この病気が臨床的に大きな課題を有する難病であることをもっと多くの人に知っていただく必要があり、そのことで病態の解明が進むと思います。わが国は今、政治の面で大きく変化しつつありますが、難病とその患者様の状況は変わりません。今後も国としての継続的な取り組みが期待されます。また現場の私も研究班の先生方とともに褐色細胞腫の患者さんの力になるとともに、その解明に微力ながら努めてゆきたいと思います。（談）

褐色細胞腫の遺伝子診断の現状と課題

成瀬光栄[*1]　田辺晶代[*1*2]　櫻井晃洋[*3]
竹越一博[*4]

要　旨

褐色細胞腫の多くは完治する良性疾患であるが，約 10～20% は悪性褐色細胞腫で予後不良である．最大の課題は確実な早期診断法がないことであり，遠隔転移で初めて診断される．最近，病態の遺伝的基盤が注目されており，特にコハク酸脱水素酵素サブユニットB（SDHB）と悪性との関連が示唆され，臨床的有用性が期待されている．今後，解析による利益と予想される課題に配慮して，長期のフォローアップ体制を構築する必要がある．

はじめに

褐色細胞腫は治癒可能な内分泌性高血圧の代表的疾患の1つである．カテコールアミンの測定と画像診断の進歩，さらに内視鏡的副腎摘出術の進歩により，その診断と治療は確立されたと考えられている．事実，我々内科医は典型的な「良性で単発性」の褐色細胞腫を経験する機会は減少しているとの印象がある．しかし一方で，近年になり，遠隔転移を呈した悪性褐色細胞腫の症例を経験することが少なくない．悪性褐色細胞腫は ① 診断初期の良悪性の診断が困難で，多発性転移で初めて悪性と判明する，② 悪性の診断後にも有効な治療法がない，③ 比較的若年者に多く，進行性に増悪，入退院の反復により患者，家族の医療費・精神面での負担が極めて大きいなど，臨床的に大きな課題を有する難治性疾患である[1]．本稿では，良悪性の鑑別診断，早期診断の面から注目されている褐色細胞腫遺伝子の異常について概説する．

*1 国立病院機構京都医療センター
内分泌代謝高血圧研究部 部長
*2 東京女子医科大学 第二内科 講師
*3 信州大学 遺伝医学・予防医学 准教授
*4 筑波大学 臨床分子病態検査医学 准教授

キーワード：褐色細胞腫関連遺伝子，
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腹部パラガングリオーマ，
悪性褐色細胞腫，Open-pheonet

褐色細胞腫と遺伝

従来から褐色細胞腫は 10% 病と呼ばれ，約 10% が悪性，両側性，多発性，遺伝性であることが知られてきた．しかし，近年の研究では全褐色細胞腫の約 25% に胚細胞遺伝子変異を認めること，散発性褐色細胞腫であっても 10～15% に遺伝子変異を認めること，特に 20 歳以下の若年者では 50% 以上に変異を認めることが報告されている[2～4]．本疾患に関連する遺伝子としては多発性内分泌腫瘍症（MEN）と関連する *RET*，von Hippel-