A pediatric pheochromocytoma presented as a multi-organ failure syndrome and brief discussion of the related medical literature

Wen Li[1] **MD,**
Chao Ma[2] **MD, PhD,**
Lingyu Zhang[3] **MD,**
Jinming Yu[4] **PhD**

1. School of Medicine. Jinan, China Department of Nuclear Medicine, Qianfo Shan Hospital Affiliated to Shandong University, Jinan, 250014, China
2. Nuclear Medicine, Affiliated Xinhua Hospital, School of Medicine Shanghai Jiaotong University, Shanghai, China
3. Department of Nuclear Medicine, Qianfo Shan Hospital Affiliated to Shandong University, China
4. Department of Radiation Oncology, Shandong Cancer Hospital affiliated to Shandong University, Jinan, China

Keywords: - Pediatric pheochromocytoma
-Multi-organ failure
-Clinical presentations
-Laboratory findings
- Renal scintigraphy

Corresponding author:
Jinming Yu PhD
Department of Radiation Oncology,
Shandong Cancer Hospital and Institute, Jinan, Shandong, China
Tel: +86-13806406293
E-mail: sdyujinming@126.com

Received:
26 April 2016
Accepted revised:
20 May 2016

Abstract
A 9 years old boy presented to our hospital complaining of night sweat and weight loss (5kg) for 3 months followed by cough, nausea, vomiting and malaise for two weeks. During that time he was found to have continuous hypertension. The clinical, electrocardiogram (ECG), renal scintigraphy and biologic findings suggested multi organ-failure syndrome. Computed tomography (CT) and ultrasound revealed a right adrenal tumor. Vanillymandelic acid (VMA) in the 24 hours urine sample was not elevated. Pheochromocytoma was suspected given his hypertension, ultrasound and CT findings. Pre-operative stabilization of his blood pressure was achieved over the following 4 weeks, after treatment with alpha- and beta-blockers, sodium nitroprusside and diuretics. Subsequently, right adrenalectomy was successfully performed. Histological examination showed that the tumor was a pheochromocytoma. Technetium-99m-ethylene dicysteine (^{99m}Tc-EC) renal scintigraphy confirmed severe kidney function impairment. *In conclusion*: Our pediatric case of pheochromocytoma was first presented, with cardiac, renal and hepatic failure which prompted us to the diagnosis of pheochromocytoma .

Hell J Nucl Med 2016; 19(2): 159-163 *Epub ahead of print: 22 June 2016* *Published online: 2 August 2016*

Introduction

Pheochromocytomas (PCC) derive from chromaffin cells of the sympathetic nervous system and produce excessive amounts of catecholamines, which are responsible for hypertensive surges, palpitations, headache, and diaphoresis commonly found with these tumors [1]. Pheochromocytoma in the pediatric population is rare with an incidence of 2 per million [2]. Etiopathogenesis, management, and outcome of pediatric PCC is still obscure because of limited number of cases studied [3-5]. Appropriate evaluation and management are essential for a favorable outcome. Despite its low incidence, PCC is the most frequent endocrine tumor in childhood [2, 6], usually appearing at the age of 8 or 9 years. Almost 10% of the cases will have a family history because of the association of PCC to multiple endocrine neoplasm syndromes [7]. Pheochromocytoma is a potentially lethal cause of childhood hypertension. Pheochromocytoma with multi-organ failure syndrome has been reported in adults [1, 8, 9] but not in children. We report a pediatric PCC with multi-organ failure as an initial presentation which was successfully treated by surgery.

Case Report

A 9 years old boy presented to our hospital complaining of night sweating and weight loss (5kg) during the last 3 months followed by cough, nausea, vomiting and malaise for the last two weeks. He had no family history. He reported bronchitis treated for 4 days with a nonsteroidal anti-inflammatory agent but had no improvement for his cough and night sweat. On examination, he had no fever and no abdominal pain. His vital signs included a heart rate of 115 beats per minute, blood pressure of 130/90mmHg, respiratory rate of 20 breaths per minute, and blood oxygen saturation of 98%. His examination was unremarkable for cardiac abnormalities. His lungs clinical examination was normal and his lower extremities were nonedematous.

Initial laboratory values revealed elevated: creatinine, urea nitrogen, troponin and B-type natriuretic peptide (proBNP) levels (Table 1). Immunological markers including antiglomerular basement membrane antibody, anti-double-stranded DNA antibody and antinuclear antibody were negative. Electrocardiogram (ECG) showed a sinusal tachycardia, T waves inverted in leads II, III, V5 and aVF, QT prolongation. Echocardiography, M type, revealed enlargement of the left atrium and left ventricle (LV) with hypokinesia and low ejection fraction (EF) of 40%. Blood pressure and LVEF are listed in Table 2. Chest radiogram showed patchy infiltrations in left lung. The clinical, ECG and biologic findings suggested multiorgan-failure syndrome: cardiac failure (increased troponin and proBNP, decreased LVEF), renal failure (creatinine, 166.5μmol/L and markedly decreased effective renal plasma flow (ERPF) by renal dynamic scintigraphy), hepatic cytolysis (alanine aminotransferase, 134IU/L) and intravascular disseminated coagulation (fibrin degradation products 7.59mg/L, thrombin time 30%). The 24h urine sample of VMA was not elevated. Despite multiple organ failure, the hemodynamic state was stable. An abdominal ultrasound (US) revealed a 45mm×34mm solid lesion at the right adrenal gland and diffuse hyperecho in both kidneys (Figure 1). Plain and enhanced computerized tomography (CT) showed a 42×33cm round mass at the right adrenal gland with inhomogenous enhancement (Figure 2a-2b). These findings were compatible with a PCC. Plain and enhanced CT also showed decreased density on both kidneys with inhomogenous enhancement especially on the left kidney (Figure 2c-2d). Pheochromocytoma was suspected given his hypertension, the US and CT imaging findings. Renal dynamic imaging using ^{99m}Tc-EC showed reduced and inhomogenous radioactivity in the right kidney and atrophy of the left kidney (Figure 3a) with markedly decreased ERPF (Figure 3b).

The patients was preoperativly treated with teicoplanin for lung infection, with supportive liver protection therapy, and for heart failure with milrinone, alpha-blockers (phentolamine, doxazosin), a beta-blocker (propranolol), sodium nitroprusside, and diuresis medication including pironolactone and hydrochlorothiazide. Before operation, blood pressure was stabilized during 4 weeks.

Subsequently, right adrenalectomy was successfully performed. Histological examination showed that the tumor was a PCC (Figure 4). Pathology features did not suggest of malignancy. There were no complications related to surgery. After right adrenalectomy, the blood pressure was restored to normal (Table 2), and patient's symptoms of severe headaches was reduced. Furthermore, his renal function improved (Table 1).

Discussion

Hypertension is increasingly recognized as a public health issue for children and adolescents. The prevalence of hypertension in children is estimated to be approximately 1%-3% [1]. The causative factors for hypertension include re-

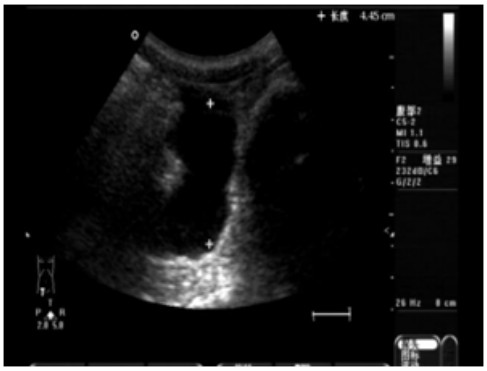

Figure 1. Abdominal ultrasound revealed a 45mm×34mm solid lesion at the right adrenal gland.

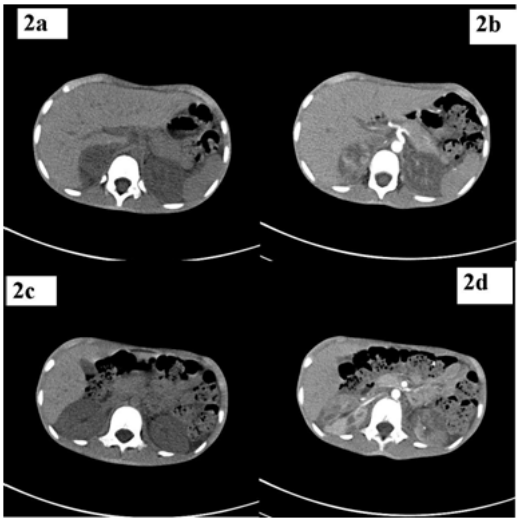

Figure 2. Plain and enhanced computerized tomography confirmed a 42×33cm round mass at the right adrenal gland with inhomogenous enhancement (Figure 2a-2b); Decreased density at both kidneys with inhomogenous enhancement especially in the left kidney were also shown by plain and enhanced CT (Figure 2c-2d).

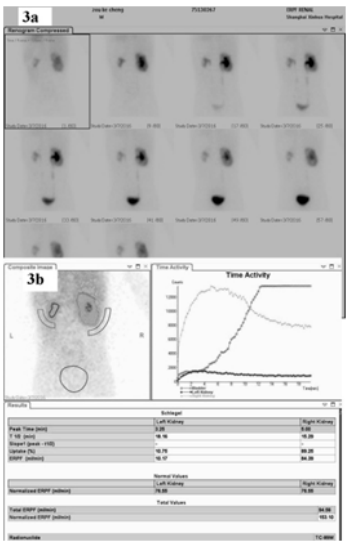

Figure 3. ^{99m}Tc-EC renal dynamic imaging (120 seconds per frame) showed reduced and inhomogeneous radioactivity in the right kidney and atrophy in the left kidney (Figure 3a) which had a markedly decreased ERPF (Figure 3b).

Table 1. *Laboratory values throughout the patient's hospital course*

Month/day	2/24	2/27	2/29	3/1	3/3	3/5	3/7	3/11	3/17
Troponin (<0.03ng/mL)	7.52	6.36	2.684	1.720	0.802	0.211	0.130	0.028	
Urine red blood cells (<25/UL)	150	150	50	150	25	50	25	25	
Erythrocyte sedimentation rate (0-15mm/h)	72			52					42
C-reactive protein, mg/L(<8mg/L)	73	60		55.59					
24-h urine VMA (2-18years old, <5.0mg/24h)				2.59/1300mL			1.9/1500mL		
proBNP (<285)	>35000	14196	12311	8876				3032	
Creatinine (62-133umol/L)	180.6	166.5	128.8	141.7	104	97.7	94.4	77.2	57.2
Urea nitrogen (2.5-7.1mol/L)	14.6	12.4	8.6	8.6	12	11.4	10.4	10	11.8
Fibrin degradation products (0-5mg/L)	7.59	7.9						2.34	
Fibrous protein (2-4g/L)	5.83	4.53						3.01	
Alanine aminotransferase (9-72U/L)	134	98	66		48	54			34
Aspartate amino transferase (38-126U/L)	118	88	31		78	53			52

VMA: Vanillylmandelic acid; ACTH: Adrenocorticotropic hormone. On day 1: ACTH: 13.03pg/mL, Cortisol compound F: 505nmol/L. At 3.23 Troponin: 0.101

Table 2. *Vital signs and ejection fraction of the left ventricle (LVEF) by M type echocardiography throughout the patient's hospital course*

Month/day	2/24	2/27	3/1	3/4-6	3/7-10	3/16-19	3/23-28
Heart rate per minute	106	108	112	102-118	100-109	99-105	
Blood pressure (mm Hg)	130/90	132/96	109-124/ 80-87	120-160/ 80-110	120-140/ 70-90	95-124/ 63-83	107-118/ 63-72
Respiratory rate per minute	28	29	32	26-32	20-22	19-22	
LVEF (%)	40		48	49	46	46	

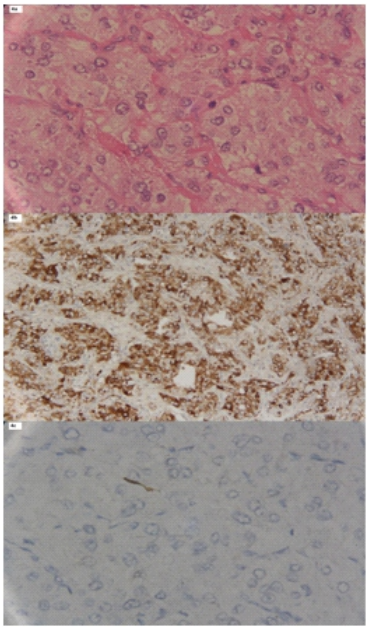

Figure 4. HE staining (X400) showed that the pheochromocytoma cells were arranged in an alveolar manner forming nests (Figure 4a). Immunohistochemistry revealed positive CgA (Figure 4b) and S100 in tumor cells (Figure 4c).

nal artery stenosis and coarctation of the aorta, hyperthyroidism, adrenogenital syndrome, Conn's and Cushing's syndromes, brain tumors, and frequently essential hypertension [7]. Pheochromocytoma is a potentially lethal cause of childhood hypertension and accounts for about 1% of pediatric hypertensive patients [3]. Pheochromocytoma is common in preadolescent boys and teenage girls [2,10-14]. Most of the tumors are right sided (n=6/16) as also in our case. Sporadic cases of PCC in children account in 14/16 of patients [14] as in our case. The typical triad of symptoms in PCC consists of episodic headache, sweating, and palpitations, but the clinical presentation in children may be different [2]. Pheochromocytoma may be completely asymptomatic as showed in a case by Eren (2015) [2]. Our case had no abdominal palpitations. In children PCC is different from adults. More often is multifocal and extra-adrenal [13,15]. Hypertension in children may be continuous rather than paroxysmal [2], as was in our case.

Multi-organ failure syndrome due to PCC with renal failure [16], acute myocardial infarction, cardiac arrhythmias, and heart failure [1, 9], pulmonary hemorrhage, and cyclic hypotension [1, 17-19], shock, rhabdomyolysis, hepatic cytolysis, acute pancreatitis, and intravascular disseminated coagulation [8] has been reported in adults. In adults, PCC related shock may be due to extensive intravascular volume depletion, hypocalcemia, and desensitization of adrenergic receptors [20]. The mechanism of renal injury is presumed to be intense vasoconstriction induced by catecholamines, leading to muscle ischemia [20, 21]. In children, PCC with rhabdomyolysis is an unusual manifestation [22]. Elevated serum BUN, creatinine and renal dynamic imaging using ^{99m}Tc-EC in our case, confirmed severe kidney function impairment. However, conventional imaging including ultrasound and CT could not suggest renal insufficiency but showed abnormal echo and density in both kidneys in our case. Renal scintigraphy can identify renal function impairment. In adults, most cases of cardiomyopathy with PCC result in partial or complete remission after treatment. The majority of cases of dilated cardiomyopathy improve within 6 weeks to 16 months to improve [23]. Our patient had slightly enlarged left atrium and ventricles, hypokinesia and 40% LVEF on presentation, with improvement to 49% when discharged. Our patient's renal failure also improved. Our pediatric case of PCC with cardiac, renal and hepatic failure is the first one reported according to our knowledge and emphasizes the importance of early diagnosis [9].

Pheochromocytoma tumors may overproduce norepinephrine and/or epinephrine [24]. The diagnosis of PCC is based on serum and urinary levels of catecholamines or their metabolites [2]. The combination of urinary metanephrines and vanillylmandelic acid (VMA) was reported to have a diagnostic sensitivity of 98% in detecting PCC [14, 25, 26]. Large tumors had the highest levels of urinary VMA [27]. Plasma free and urinary metanephrines and also total metanephrines were performed equivalently for diagnosing PCC in 46 adult cases without renal insufficiency [24]. Urinary VMA was reported to be elevated in 53%, and epinephrine and norepinephrine in 42% in a total of 19 pediatric patients with PCC [28]. Patients with chronic renal failure can not often take the 24 hours urine collection test which makes it difficult to diagnose PCC in patients with end stage renal disease [29]. In our case the VMA in the 24 hours collected urine was not elevated which may be due to renal insufficiency.

In addition, ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and iodine-123-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy are useful for the localization of PCC [14]. Magnetic resonance imaging is currently the best tool for tumor localization [13]. The accuracy of these techniques is enhanced considerably when a morphologic study (CT or MRI) is combined with a functional study such as ^{123}I-MIBG scintigraphy [30]. Planar $^{123/131}$I-MIBG or single photon emission tomography (SPET)/CT scans were used in both children and adults specifically for the detection of atypically located PCC, for distant metastases, and for recurrences [25, 26, 30, 31]. Other researchers showed that somatostatin receptors imaging using gallium-68 (^{68}Ga)-DOTA(0)-tyr(3)-octreotate (^{68}Ga-DOTATATE) was better for the localization of sporadic metastatic PCC as compared to fluorine-18-fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET/CT, and CT/MRI [32].

When a PCC is suspected in a child, careful and expeditious management is essential to prevent complications or even death. Pre- intra- and postoperative medical management is as important as the surgical procedure [14, 15]. Malignancy in PCC is very difficult to diagnose histologically, so the biologic behavior of the tumor may determine its classification. Pediatric malignant PCC actually is very rare ranging from 8.3% to 13.1% which is lower than that in adults (ranging from 32% and 42%) [14]. Tumor size may be an indicator of malignant potential. It has been reported that

benign tumors had a mean diameter of 45±4mm as in our case, whereas malignant tumors, 86±13mm [6].

Recurrence of PCC is very important from the clinical point of view. Children who experience recurrence will usually develop recurrent symptoms within a year of diagnosis. The presence of extra-adrenal cells in tissues where chromaffin cells are not normally found indicates metastatic disease. The incidence of PCC recurrence varies from 10% to 40% [26, 33]. There were no specific clinical or laboratory data in our patient to predict recurrence [14]. Interestingly, a rare case of adrenal insufficiency following unilateral adrenalectomy of a PCC was reported in a 10 years old child which may be explained that PCC had dual-hormone (also adrenocorticotropic hormone ACTH) secreting capacity, and that the child had unrecognized subclinical Cushing's syndrome pre-operatively [34]. Our case had normal ACTH and no indications of Cushing's syndrome.

In conclusion, our patient exhibited a rare kind of PCC complicated by renal, cardiac and hepatic failure, which was successfully treated by laparoscopic surgery. Technetium-^{99m}Tc-EC renal dynamic imaging not only revealed kidney atrophy, but also severe kidney impairment better than US or contrast enhanced CT. This case, according to our knowledge, is first reported and emphasizes the importance to diagnose PCC in case of an unexplained multi-organ failure syndrome so as to reduce mortality.

Acknowledgment
This work was supported by the Development of Science and Technology Project of Shandong Province (2013GGB14067)

Bibliography

1. Park M, Hryniewicz K, Setaro JF. Pheochromocytoma presenting with myocardial infarction, cardiomyopathy, renal failure, pulmonary hemorrhage, and cyclic hypotension: case report and review of unusual presentations of pheochromocytoma. *J Clin Hypertens (Greenwich)* 2009; 11: 74-80.
2. Eren E, Saglam H, Caliskan Y et al. Pediatric patients with pheochromocytoma: Experience of a tertiary health center. *Pediatr Int* 2015; 57: 875-9.
3. Pickard JL, Ross G Jr., Silver D. Coexisting extraadrenal pheochromocytoma and renal artery stenosis: a case report and review of the pathophysiology. *J Pediatr Surg* 1995; 30: 1613-5.
4. Ein SH, Shandling B, Wesson D et al. Recurrent pheochromocytomas in children. *J Pediatr Surg* 1990; 25: 1063-5.
5. Ein SH, Weitzman S, Thorner P et al. Pediatric malignant pheochromocytoma. *J Pediatr Surg* 1994; 29: 1197-201.
6. Pham TH, Moir C, Thompson GB et al. Pheochromocytoma and paraganglioma in children: a review of medical and surgical management at a tertiary care center. *Pediatrics* 2006; 118: 1109-17.
7. Newman KD, Ponsky T. The diagnosis and management of endocrine tumors causing hypertension in children. *Ann N Y Acad Sci* 2002; 970: 155-8.
8. Herbland A, Bui N, Rullier A et al. Multiple organ failure as initial presentation of pheochromytoma. *Am J Emerg Med* 2005; 23: 565-6.
9. Tamdy A, Oukerraj L, Khatri D et al. Acute myocardial infarction revealing a pheochromocytoma: a case report. *Ann Cardiol Angeiol (Paris)* 2010; 59: 97-9.
10. Kaufman BH, Telander RL, van Heerden JA et al. Pheochromocytoma in the pediatric age group: current status. *J Pediatr Surg* 1983; 18: 879-84.
11. Walther MM, Keiser HR, Linehan WM. Pheochromocytoma: evaluation, diagnosis, and treatment. *World J Urol* 1999; 17: 35-9.
12. Waguespack SG, Rich T, Grubbs E et al. A current review of the etiology, diagnosis, and treatment of pediatric pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab* 2010; 95: 2023-37.
13. Ross JH. Pheochromocytoma. Special considerations in children. *Urol Clin North Am* 2000; 27: 393-402.
14. Ciftci AO, Tanyel FC, Senocak ME, Buyukpamukcu N. Pheochromocytoma in children. *J Pediatr Surg* 2001; 36: 447-52.
15. Reddy VS, O'Neill JA Jr, Holcomb GW 3rd et al. Twenty-five-year surgical experience with pheochromocytoma in children. *Am Surg* 2000; 66: 1085-91; discussion 1092.
16. Fujiwara M, Imachi H, Murao K et al. Improvement in renal dysfunction and symptoms after laparoscopic adrenalectomy in a patient with pheochromocytoma complicated by renal dysfunction. *Endocrine* 2009; 35: 57-62.
17. Dinckal MH, Davutoglu V, Soydinc S et al. Phaeochromocytoma-induced myocarditis mimicking acute myocardial infarction. *Int J Clin Pract* 2003; 57: 842-3.
18. Attar MN, Moulik PK, Salem GD et al. Phaeochromocytoma presenting as dilated cardiomyopathy. *Int J Clin Pract* 2003; 57: 547-8.
19. Kimura Y, Ozawa H, Igarashi M et al. A pheochromocytoma causing limited coagulopathy with hemoptysis. *Tokai J Exp Clin Med* 2005; 30: 35-9.
20. Hamrin B. Sustained hypotension and shock due to an adrenaline-secreting phaeochromocytoma. *Lancet* 1962; 2: 123-4.
21. Imperadore F, Azzolini M, Piscioli F et al. A rare cause of cardiogenic shock: catecholamine cardiomyopathy of pheochromocytoma. *Ital Heart J* 2002; 3: 375-8.
22. Celik H, Celik O, Guldiken S et al. Pheochromocytoma presenting with rhabdomyolysis and acute renal failure: a case report. *Ren Fail* 2014; 36: 104-7.
23. Lin PC, Hsu JT, Chung CM, Chang ST. Pheochromocytoma underlying hypertension, stroke, and dilated cardiomyopathy. *Tex Heart Inst J* 2007; 34: 244-6.
24. Grouzmann E, Drouard-Troalen L, Baudin E et al. Diagnostic accuracy of free and total metanephrines in plasma and fractionated metanephrines in urine of patients with pheochromocytoma. *Eur J Endocrinol* 2010; 162: 951-60.
25. Lucon AM, Pereira MA, Mendonca BB et al. Pheochromocytoma: study of 50 cases. *J Urol* 1997; 157: 1208-12.
26. Bravo EL. Evolving concepts in the pathophysiology, diagnosis, and treatment of pheochromocytoma. *Endocr Rev* 1994; 15: 356-68.
27. Sawin RS. Functioning adrenal neoplasms. *Semin Pediatr Surg* 1997; 6: 156-63.
28. Bhansali A, Rajput R, Behra A et al. Childhood sporadic pheochromocytoma: clinical profile and outcome in 19 patients. *J Pediatr Endocrinol Metab* 2006; 19: 749-56.
29. Maeda T, Kozakai N, Nishiyama T et al. [Pheochromocytoma with chronic renal failure: a case report]. *Hinyokika Kiyo* 2009; 55: 409-12.
30. Pattou FN, Combemale FP, Poirette JF et al. Questionability of the benefits of routine laparotomy as the surgical approach for pheochromocytomas and abdominal paragangliomas. *Surgery* 1996; 120: 1006-11; discussion 1012.
31. Sharma P, Dhull VS, Jeph S et al. Can hybrid SPECT-CT overcome the limitations associated with poor imaging properties of ^{131}I-MIBG?: Comparison with planar scintigraphy and SPECT in pheochromocytoma. *Clin Nucl Med* 2013; 38: e346-53.
32. Janssen I, Chen CC, Taieb D et al. ^{68}Ga-DOTATATE PET/CT in the Localization of Head and Neck Paragangliomas Compared with Other Functional Imaging Modalities and CT/MRI. *J Nucl Med* 2016; 57: 186-91.
33. Marshall DG, Ein SH. Two boys with four pheochromocytomas each. *J Pediatr Surg* 1986; 21: 815-7.
34. Sjoeholm A, Li C, Leem C et al. Adrenal insufficiency in a child following unilateral excision of a dual-hormone secreting phaeochromocytoma. *Endocrinol Diabetes Metab Case Rep* 2015; 2015: 150041.