Case Report

Primary Intrarenal/Perirenal Neuroblastoma Mimicking Wilms' Tumor at Presentation in a 5-Year-Old Girl: A Case Report from Siriraj Hospital

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Primary intrarenal/perirenal neuroblastoma (NB) is NB that primarily arises in intrarenal and/or perirenal regions. Regarding its location, this tumor can mimic Wilms' tumor, a more common pediatric renal tumor, at presentation. Owing to difference in clinical management and prognosis, it is crucial to distinguish primary intrarenal/perirenal NB from Wilms' tumor at the time of diagnosis. Recognition of its characteristic features, which are distinctive from its adrenal counterpart, is helpful to guide to the correct diagnosis and proper treatment. However, due to its rarity with less than 100 cases described in English literatures, the characteristics of primary intrarenal/perirenal NB have not been widely studied. The authors, therefore, report this case of primary intrarenal/perirenal NB, which occurred in right kidney of a 5-year-old Thai girl in order to illustrate the characteristic features of this tumor. To the authors' knowledge, this case is the first case of primary intrarenal/perirenal NB that has been reported in Thailand.

Keywords: *Neuroblastoma, Intrarenal neuroblastoma, Perirenal neuroblastoma*

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Neuroblastoma (NB) is the most primitive tumor in the family of neuroblastic neoplasms, which arise from the primitive precursor cells of the sympathetic nervous system[1,2]. It is the most common solid tumor of the childhood with median patient's age of approximately two years[3,4]. In Thailand, it is the fourth most common childhood cancer with age-adjusted incidence rate of 4.9 per million[5]. Commonly NB originates from the medulla of adrenal gland or along the area where the sympathetic nervous system is found. However, a small proportion can primarily originate in intrarenal and/or perirenal areas and, thus, clinically mimic Wilms' tumor, a more common pediatric renal tumor, at presentation. To the authors' knowledge, less than 100 cases of primary intrarenal/perirenal NB in children had been reported in English literatures[6-17].

Owing to difference in clinical management and prognosis, it is crucial to distinguish primary intrarenal/perirenal NB from Wilms' tumor at the time of diagnosis. Recognition of features that are characteristic to primary intrarenal/perirenal NB or helpful to distinguish primary intrarenal/perirenal NB from Wilms' tumor is important to avoid misdiagnosis. However, due to its rarity, the characteristics of primary intrarenal/perirenal NB have not been widely studied. In addition, to the authors' best knowledge, none of such cases have been reported in Thailand. The authors, therefore, report this case of primary intrarenal/perirenal NB, which occurred in right kidney of a 5-year-old Thai girl in order to illustrate the characteristic features of this tumor.

Case Report

A 5-year-old girl presented with progressive abdominal distension for three months. Physical

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examination revealed a right-sided abdominal mass without other remarkable findings. Laboratory investigations revealed increased serum neuron-specific enolase (NSE) (108.5 ng/mL; reference range 0-15.2 ng/mL), and normal serum alpha-fetoprotein (2.09 IU/mL; reference range 0-5.8 IU/mL). Contrast-enhanced computed tomography (CECT) of the whole abdomen showed a large, heterogeneously-enhanced, hypodensity retroperitoneal mass that likely originated from intrarenal and/or perirenal regions of the right kidney. The mass measured 7.8x10x13 cm. Extension of the mass across the midline as well as encasement of inferior vena cava (IVC) and aorta was noted (Fig. 1). The right adrenal gland was unremarkable. No evidence of metastatic disease was detected by computed tomography (CT) of the chest, Tc-99m whole body bone scan, bone marrow aspiration and bone marrow biopsy. The diagnosis of Wilms' tumor was suspected preoperatively. The patient underwent right nephrectomy. A lobulated mass, approximately 10x14 cm in size, was identified intraoperatively in the right-sided retroperitoneum. The tumor involved middle part and lower pole of the right kidney and extended downward toward the level of aortic bifurcation. Extension of the tumor across the midline to the left side of the aorta was also noted. Enlarged right renal hilar, aortic bifurcation, and left para-aortic lymph nodes were observed. Renal vessels, abdominal aorta, and IVC were not involved by the tumor. Neither liver nor peritoneal metastasis was identified. Right adrenal gland was readily identified and was unremarkable.

Gross examination of the right nephrectomy specimen revealed a large encapsulated and multilobulated mass that replaced the middle part and lower pole of the kidney and involved the renal hilum and perirenal soft tissue. The mass measured 14x11x9.5 cm. Its cut surfaces mostly showed soft, hemorrhagic dark brown and light tan tissues with focal areas of necrosis and cystic change (Fig. 2).

Microscopically, the tumor was composed of undifferentiated neuroblastic cells with a salt and pepper chromatin pattern. Neuropil formation was focally noted in the background (Fig. 3A). All of the findings mentioned above were compatible with poorly differentiated NB. The mitosis-karyorrhexis index (MKI) was intermediate (150/5,000 cells). Regarding the patient's age, MKI and the histological subtype of NB, this tumor was classified in "unfavorable histology" group according to the International Neuroblastoma Pathology Prognostic Classification (INPC)[18,19]. Microcalcification was not identified. At the interface between the tumor and the uninvolved renal parenchyma, the tumor was well demarcated and surrounded by fibrous capsule (Fig. 3B). Invasion into the renal hilar soft tissue was observed (Fig. 3C). Biopsied right renal hilar, aortic bifurcation, and left para-aortic lymph nodes were positive for the metastatic tumors (Fig. 3D).

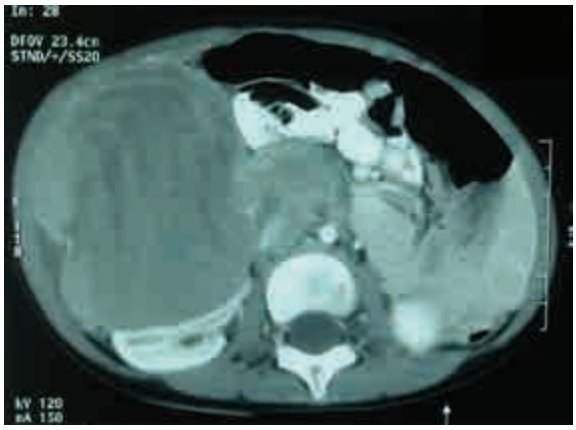

Fig. 1 Contrast-enhanced computed tomography (CECT) of the whole abdomen showed a large, heterogeneously-enhanced, hypodensity retroperitoneal mass that likely originated from intrarenal and/or perirenal regions of the right kidney. Midline crossing and encasement of the inferior vena cava and abdominal aorta were observed.

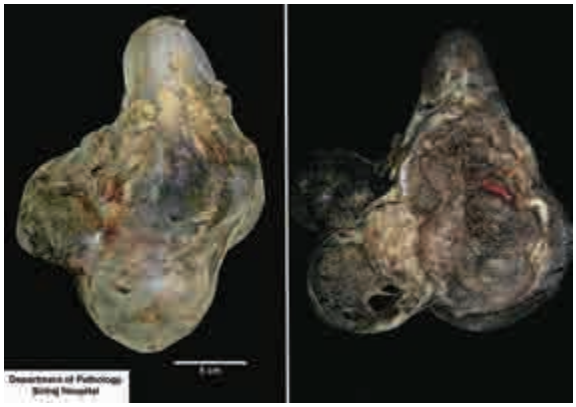

Fig. 2 The right nephrectomy specimen showed a large encapsulated and multilobulated mass that replaced the middle part and lower pole of the kidney. Involvement of the renal hilum and surrounding perirenal soft tissue was observed. Cut surfaces of the tumor revealed soft, hemorrhagic, dark brown and light tan tissues with focal areas of tumor necrosis and cystic change. No calcification was identified.

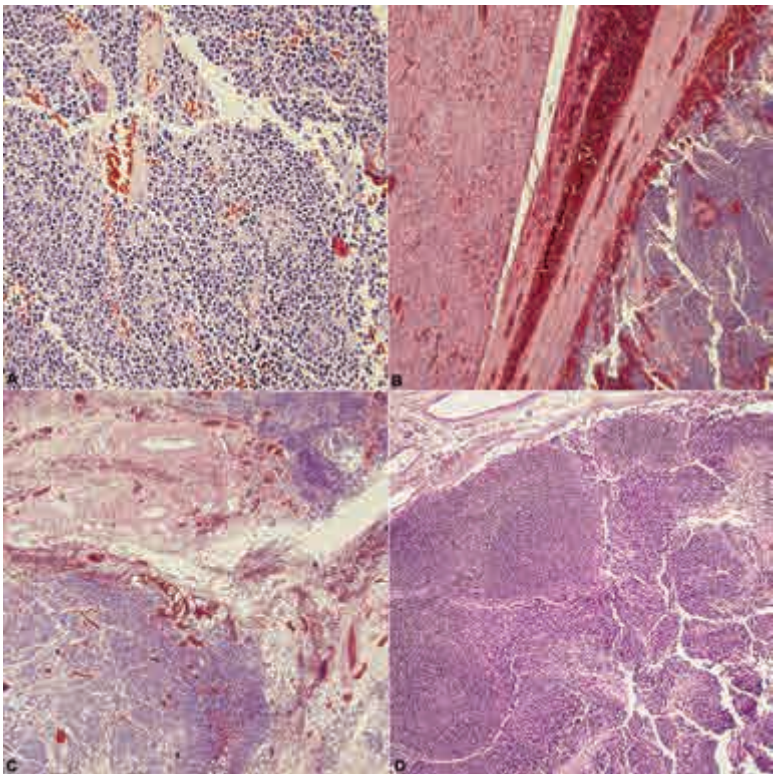

Fig. 3 Histological findings of primary intrarenal/perirenal neuroblastoma (NB). A) Sections of the tumor showed undifferentiated neuroblastic cells in the background of neuropil, compatible with poorly differentiated NB (hematoxylin and eosin, x200). B) The interface of the tumor with uninvolved renal parenchyma showed well circumscription of the tumor with fibrous encapsulation (hematoxylin and eosin, x40). C) Tumor infiltration into the renal hilar fat was noted (hematoxylin and eosin, x40). D) The biopsied left para-aortic lymph node showed metastatic poorly differentiated NB (hematoxylin and eosin, x100).

After the surgery, diagnostic workup for staging was planned. However, due to a constrained schedule, Iodine-131 metaiodobenzylguanidine (I-131 MIBG) scintigraphy could not be performed before starting chemotherapy. Therefore, the patient was diagnosed to have at least a stage III disease and four courses of postoperative induction chemotherapy (cisplatin, etoposide, doxorubicin, and cyclophosphamide) were administered upfront. After completion of the induction chemotherapy, I-131 MIBG scintigraphy and CT scan of the abdomen revealed no evidence of the residual tumor at the surgical bed and elsewhere and serum NSE level was 8.97 ng/mL. Local radiotherapy to the tumor bed (total dose of 2,160 cGy) as well as maintenance chemotherapy (cyclophosphamide and doxorubicin alternating with cisplatin and etoposide) was subsequentially provided. The fourteenth month of maintenance chemotherapy was just completed by the time of the present report and the patient was clinically well at 22 months after the surgery. The most recent serum NSE level was 10.75 ng/mL. The results of the latest CT scan of the abdomen and I-131 MIBG scintigraphy were unremarkable. The treatment plan is to continue maintenance chemotherapy for 20 months, then follow by a regular follow-up with periodic testing for serum NSE level and CT scan of the abdomen.

Discussion

Primary renal NB is a rare clinical entity. It is originally believed to arise from either the entrapped developmental remnant of adrenal medullary tissue in the kidneys or the intrarenal sympathetic ganglion[14,20]. Thus, by strict definition, the tumor should be confined to the kidney or clearly demonstrated evidence supporting intrarenal tumor[21]. However, the majority of previously reported primary renal NB cases initially presented with a large mass with extensive involvement of perirenal soft tissue (mean and median size of

8.9 and 8.65 cm, respectively, according to 14 reported cases with available information of tumor size and tumor extension)[7,8,10-13,17], which was difficult to precisely determine whether the tumor truly had an epicenter in the kidney. Moreover, Fan R has recently demonstrated high frequency of renal hilar involvement in this type of NB, which might suggest perirenal origin[7]. The authors, therefore, hypothesize that the so-called "primary renal NB" might actually represent NB that arises either from intrarenal or perirenal area. In the current case, the tumor was large (14 cm in maximum diameter) and showed involvement of both renal parenchyma and perirenal soft tissue which was difficult to determine its precise origin, but definitely not originating from the ipsilateral adrenal gland. This finding was also observed in the previously reported cases. Therefore, the authors prefer to describe the tumor in this particular case as well as others that had the same feature as the primary intrarenal/perirenal NB in order to convey its ambiguity of origin.

Clinically primary intrarenal/perirenal NB has some characteristic features, which are distinctive from its more common adrenal counterpart. Firstly, primary intrarenal/perirenal NB tends to have a slightly older age at presentation comparing with NB arising in adrenal gland (32 months[9] versus approximately 24 months[3,4]). Also it appears that, among cases of primary intrarenal/perirenal NB, girls tend to present at an older age than boys (mean age 30 months versus 20.4 months; median age 36 months versus 15.5 months)[7,8,10,12-14,17]. Secondly, hypertension is more common in primary intrarenal/perirenal NB comparing to NB that occurs in other sites (62.5%[7,8,10,12-14,17] versus 10 to 27%[22,23]). The majority of cases that presented with hypertension usually had elevated serum and/or urine catecholamine metabolites[7,8,10,12-14,17]; this might suggest that hypertension in primary intrarenal/perirenal NB is mainly a result of the vasoconstrictive catecholamines that are secreted by the tumor and checking serum and/or urine catecholamine metabolites might be helpful in guiding to the diagnosis. However, there are a subset of cases in which hypertension was detected without an increase in serum or urine catecholamine metabolites[7,10-12]. In such cases, hypertension might be explained by compression of renal artery by the tumor, which resulted in stimulation of renin-aldosterone system. Finally, a high-stage (stage III or IV) disease at presentation is common. In the study of Gupta and colleagues, 70% of cases initially presented with a stage III disease, and 24% with a stage IV disease[9]. In the present case, the patient presented with a high-stage disease (at least stage III) at the age of five years, which was much older than most cases of primary intrarenal/perirenal NB that had been previously reported. Partly, this might be explained by the patient's gender. Although hypertension is a common presentation in primary intrarenal/perirenal NB, it was not detected in this case. The authors speculate that the uninvolved renal artery might explain the normal blood pressure. Whether there was a production of catecholamine by the tumor or not in this case, the authors cannot address this issue since the testing for serum or urine catecholamine was not performed at the time of diagnosis.

Regarding radiological features, presence of intratumoral calcification and lacking circumscription or pseudocapsule are characteristics, which usually distinguish NB from other differential diagnoses of a retroperitoneal mass[20,24]. However, a subset of primary intrarenal/perirenal NBs, of which included the current case, did not demonstrate these characteristic features[7,25]. Therefore, in such cases, it might be difficult to be recognized as NB based on the radiological findings and might be misdiagnosed as Wilms' tumor as it happened in this case and 86% of cases in the study of Gupta and colleagues[9]. As the authors retrospectively studied this case in details in order to find any possible clues that might be helpful to avoid this preoperative diagnostic pitfall, it appears that careful observation for other radiological features, which are often seen in NB but not in Wilms' tumor such as enlargement of retrocrural or other retroperitoneal lymph nodes, extension of the tumor across the midline and encasement of retroperitoneal vessels[26], can be beneficial in guiding to the diagnosis of NB.

Of all NB histologic subtypes, poorly differentiated subtype is the most common subtype found in primary intrarenal/perirenal NBs[7,8,10-13]. In addition, anaplasia was identified in 28% of cases according to the study of Gupta and colleagues[9]. Regarding a commonness of poorly differentiated NB histologic subtype and an older age of patient at presentation (≥18 months), primary intrarenal/perirenal NB usually falls into the "unfavorable histology" group of the INPC classification, which typically suggests unfavorable clinical outcome[18,19]. In the current case, all of the features mentioned above except for the presence of anaplasia were identified.

Because primary intrarenal/perirenal NB is usually classified in the "unfavorable histology" group,

and the patient usually presents with a high-stage disease, the authors speculate that this tumor may portray a poor clinical outcome. However, the current case as well as the majority of cases in the recent study of Fan R[7] seemed to have much better outcome comparing with most of the previously reported cases. This might partly be explained by improvement of the treatment modalities for NB in the recent years. Whether primary intrarenal/perirenal NB truly has a favorable prognosis despite being classified in the "unfavorable histology" group and having a high-stage disease at presentation, the authors cannot further address this issue on the basis of this case report.

In conclusion, primary intrarenal/perirenal NB is a rare type of NB that arises in a kidney and/or a region of perirenal soft tissue. Clinically, this particular type of NB is distinctive from its more common adrenal counterpart. Owing to its location, primary intrarenal/perirenal NB can mimic Wilms' tumor, a more common pediatric renal tumor, at presentation. Awareness of its characteristic clinical features and radiological findings and careful clinical-radiological correlation are important to guide to a correct preoperative diagnosis. In case that the preoperative diagnosis is uncertain, upfront open biopsy or tumor removal for histopathological diagnosis might be needed for definitive diagnosis and treatment planning.

What is already known on this topic?

Intrarenal/perirenal NB is uncommon and can mimic Wilms' tumor, a more common pediatric renal tumor, at presentation. This type of NB seems to have some characteristic features that are distinctive from their adrenal counterpart.

What this study adds?

The current case was the first case of intrarenal/perirenal NB reported in Thailand. The tumor's histopathology is very crucial to establish the definite diagnosis and plan of treatment.

Potential conflicts of interest

None.

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มะเร็งเซลล์ประสาทนิวโรบลาสโตมาที่เกิดบริเวณเนื้อไตและเนื้อเยื่อรอบไตในเด็กหญิงอายุ 5 ปี ซึ่งมีลักษณะทางคลินิกคล้ายกับมะเร็งไตในเด็ก (Wilms' tumor): รายงานผู้ป่วยจากโรงพยาบาลศิริราช

จิตสุภา ตรีทิพย์สถิตย์, คณาพร ปราชญ์นิวัฒน์, มงคล เลาหเพ็ญแสง, จันทิมา รองวิริยะพานิช, กมล เผือกเพ็ชร, กลีบสไบ สรรพกิจ

มะเร็งเซลล์ประสาทนิวโรบลาสโตมาที่เกิดบริเวณเนื้อไตและเนื้อเยื่อรอบไตสามารถให้ลักษณะทางคลินิกที่คล้ายคลึงมะเร็งไตในเด็ก (Wilms' tumor) ได้เนื่องจากเกิดในบริเวณเนื้อไตและเนื้อเยื่อรอบไตเหมือนกัน เนื่องจากมะเร็งทั้งสองชนิดนี้มีแนวทางการรักษาและพยากรณ์โรคที่แตกต่างกัน การวินิจฉัยแยกโรคทั้งสองออกจากกันจึงมีความสำคัญอย่างยิ่ง การมีความรู้เกี่ยวกับลักษณะทางคลินิกที่สำคัญของมะเร็งเซลล์ประสาทนิวโรบลาสโตมาที่เกิดบริเวณเนื้อไตและเนื้อเยื่อรอบไต ซึ่งต่างจากมะเร็งเซลล์ประสาทนิวโรบลาสโตมาทั่วไปที่พบในต่อมหมวกไตสามารถช่วยแนะแนวทางการวินิจฉัยโรคที่ถูกต้อง และนำไปสู่การวางแผนการรักษาผู้ป่วยที่เหมาะสมได้ อย่างไรก็ตาม เนื่องจากมะเร็งเซลล์ประสาทนิวโรบลาสโตมาที่เกิดในตำแหน่งนี้พบไม่บ่อย (น้อยกว่า 100 ราย จากการทบทวนวรรณกรรมทางการแพทย์ภาษาอังกฤษ) ลักษณะทางคลินิกของมะเร็งชนิดนี้จึงยังไม่ได้รับการศึกษาอย่างกว้างขวางนัก คณะผู้รายงานจึงรายงานการพบมะเร็งเซลล์ประสาทนิวโรบลาสโตมาที่เกิดในบริเวณเนื้อไตและเนื้อเยื่อรอบไตขวาในเด็กหญิงชาวไทยอายุ 5 ปีรายนี้ โดยมีวัตถุประสงค์เพื่อศึกษาลักษณะทางคลินิกต่าง ๆ ที่สำคัญและเป็นประโยชน์ในการวินิจฉัยมะเร็งชนิดนี้ นอกจากนี้คณะผู้รายงานยังพบว่าผู้ป่วยรายนี้เป็นผู้ป่วยมะเร็งเซลล์ประสาทนิวโรบลาสโตมาที่เกิดในบริเวณเนื้อไตและเนื้อเยื่อรอบไตรายแรกของประเทศไทย