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Clinico-pathological patterns of a rare presentation of abdominal neuroblastoma in children

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ABSTRACT

Background: To study the diagnosis, management, and outcome of abdominal neuroblastoma (NBL) in infants and children and also the behavior of some rare types. **Patients and Methods:** This is a retrospective review of 46 infants and children having abdominal NBL at King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia and Tanta University Hospital, Tanta, Egypt (a joint study) between February 2008 and January 2012. The patients' medical records were reviewed for demographic details, clinical presentations, histopathology, radiological diagnosis, management, and outcome. **Results:** Of the 46 patients, 5 (10.7%), three males and two females, aged 1.5-6.5 years (mean: 4.5 years) had rare types of NBL (one bilateral NBL, one pelvic NBL, one pelvic-abdominal, and there were two cases of ganglioneuroblastoma). Three patients (two ganglioneuroblastoma and one pelvic) underwent complete surgical removal of the tumor with a good disease survival, whereas the other two patients (two bilateral and one pelviabdominal) had advanced disease and received palliative chemoradiotherapy. The remaining 41 patients, 23 males (56.1%) and 18 females (43.9%), with mean age 3.9 years (range: 1-7 years), had unilateral abdominal NBL. Twelve of them had resectable tumor and underwent primary surgical removal of the tumor, whereas the remaining 29 patients had unresectable tumor and received pre-operative chemotherapy with good response of the tumor in seven patients and no response in the remaining 22 patients. **Conclusion:** Primary complete surgical removal of tumor is advisable in localized NBL with a good outcome, whereas in advanced cases, it is better to start with pre-operative chemotherapy to downsize the tumour mass and safe delayed surgical excision. An increase in patient's age is associated with advanced stage of NBL and poor prognosis except in ganglioneuroblastoma cases due to maturation of tumor cells.

Key words: Abdominal neuroblastoma, childhood malignancies, malignant tumor, solid tumor

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INTRODUCTION

Neuroblastoma (NBL) is the most malignant tumor in children and most common solid tumor in infants accounting for 8-10% of all childhood malignancies (about 8.7 million/year). It affects primarily children younger than 10 years of age. About 50% are below the age of 2 years. It occurs more frequently in boys than in girls (1.2:1). It originates from the neural crest cell, which normally gives rise to the adrenal medulla and sympathetic ganglia anywhere from the neck to the pelvis. It occurs in the abdomen in about 70% of cases (45% in adrenal medulla and 25% in sympathetic ganglia).[1]

NBL consists of nests of neuroblasts (undifferentiated small round cells) separated by fine fibrovascular septa (stroma) and showing Rosette formation in about one-third of cases. In about 5-10% of cases, some neuroblasts show differentiation into mature ganglion cells and the tumor is classified as ganglioneuroblastoma; however, in adolescents and young adults, the tumor is formed of mature ganglion cells separated by collagenous stroma and called ganglioneuroma and this is the most benign type of NBL. NBL and ganglioneuroblastoma were classified by Shimada and recently by International Neuroblastoma Pathology Classification into favorable and unfavorable histology tumors according to the degree of neuroblasts differentiation and stromal development (stroma-rich and stroma-poor).[2] Patients with NBL may show genetic abnormalities in the form of deletion in the short arm of chromosome one and amplification of genes of chromosome two (called

N myc gene amplification) and this is considered a poor prognostic factor of the disease.[3]

The most common clinical presentation of abdominal NBL in children is a large flank mass; however, other rare presentations may include pelvic NBL, bilateral, pelviabdominal, and neonatal NBL, other manifestations may associate with the tumor mass-like metastatic lesions in bone or liver, pallor, abdominal pain, weight loss, and fever. NBL is a biologically active tumor secreting vanillylmandelic acid (VMA) and homovanillic acid, or other metabolites such as catecholamines, neuron-specific enolase (NSE), and vasoactive intestinal peptides in some cases.[1,4] NBL can be diagnosed radiologically by ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) with different sensitivities and specificities.[5]

Three major staging systems are used for staging of NBL: Evans staging system (1971), Pediatric Oncology Group (1983) system, and the widely used International Neuroblastoma Staging System (INSS 1988).[6] Treatment of NBL is a multimodality therapy composed of surgery, chemotherapy, and radiotherapy either in combination or separate depending on disease stage, patient age, genetic abnormalities, tumor biology, and histological classifications.[4,7]

MATERIALS AND METHODS

This is a retrospective review of 46 infants and children with abdominal NBL diagnosed and treated at surgery departments of King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia (19 patients) and Tanta University Hospital, Tanta, Egypt (27 patients) between February 2008 and January 2012 (a joint study). The patients' medical records were reviewed for demographic details, clinical presentations, histopathology, radiological diagnosis, management, and outcome.

The most common presenting feature in our NBL patients was abdominal mass (pelviabdominal in one) present in 45 patients (97.8 %) and the least presenting symptom was recurrent attacks of urine retention in one patient with pelvic NBL (2.2%). Other associated manifestations include pallor in 27 patients (58.7%), anorexia in 25 (54.4%), abdominal pain in 24 (52.2%), weight loss in 19 (41.3%), fever in 14 (30.4%), and hypertension, limping then paraplegia, Raccoon eye, and subcutaneous nodules each presented in 2.2% of patients [Table 1].

Abdominopelvic US and contrast CT were done in all patients and showed heterogeneous or homogenous mass arising from the suprarenal gland in 29 patients (63.04%) and from paraspinal ganglia in 17 patients (36.9%) [Figure 1]. The tumor was located on the left side in 35 cases (76.1%), on the right side in 10 cases (21.7%), and bilateral tumor arising from both adrenal glands in one patient (2.2%). We also used US and CT to obtain guided biopsies for tissue diagnosis. Intravenous urography (IVU) and contrast CT showed that the kidney on the affected side was compressed and displaced downwards by the adrenal tumor giving the picture of flower drop appearance or distorted and displaced laterally by a paraspinal tumor or the urinary bladder is compressed and displaced to the right side by a huge left pelviabdominal tumor. MRI showed higher signal intensity of the tumor on T2-weighted images and equal or lower signal intensity on T1, whereas areas of degeneration, necrosis, or hemorrhage appeared heterogeneous [Figure 2].

Table 1: Clinical presentations in 46 neuroblastoma patients

Clinical presentations	No.	%
Abdominal mass	45	97.8
Pallor	27	58.7
Anorexia	25	54.4
Abdominal pain	24	52.2
Weight loss	19	41.3
Fever	14	30.4
Recurrent attacks of urine retention	1	2.2
Hypertension	1	2.2
Limping then paraplegia	1	2.2
Raccoon eye	1	2.2
Subcutaneous nodules	1	2.2

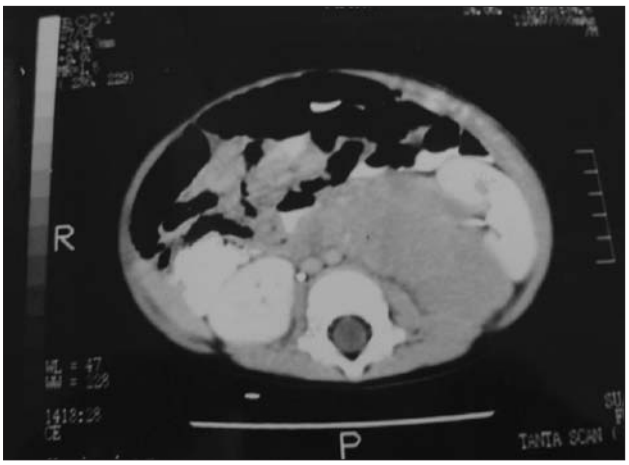


Figure 1: Computed tomography abdomen of Lt. paraspinal neuroblastoma showing a large mass crossing the mid-line, encasing aorta and IVC and displacing the Lt. kidney upwards and laterally

Urinary VMA was found elevated in 38 (82.6%) patients and serum NSE in 42 (91.3%) patients. Bone marrow (BM) aspiration/or biopsy was done in only 36 patients and found infiltrated by neuroblasts in 14 (38.9%) patients. ^{99m}Technetium bone scan was done in Egyptian patients as metaiodobenzylguanidine (MIBG) scintigraphy was not available in the institution.

In our patients, we used the INSS for staging of the tumor and surgical intervention was carried out through a transverse trans-abdominal extraperitoneal approach, gently dissecting the tumor from its surrounding structures till complete removal. In Stages I and II localized tumors, primary surgical removal of tumor was done, whereas in unresectable and very large tumors not amenable for safe primary surgical excision, biopsies was taken followed by induction (pre-operative) chemotherapy for 3-4 cycles for cytoreduction of the tumor mass and delayed surgical excision was tried.

RESULTS

After reviewing our patients' medical records from both institutions, we found the tumor completely located in the abdomen and on one side in 43 patients, pure pelvic in one, pelviabdominal in one, and bilateral in one. All patients had the classical histopathological picture of NBL [Figure 3] except two who had ganglioneuroblastoma.

Five patients (10.7%) out of 46 were found to have rare types of NBL, bilateral (one), pelvic (one), pelviabdominal (one), and ganglioneuroblastoma (two), they were three males and two females and their mean age was 4.5 years (range: 1.5-6.5), whereas the other 41 patients had conventional unilateral abdominal NBL, they were 23 males (56.1%) and 18 females (43.9%) and their mean age was 3.9 years (range: 1-7 years).

According to INSS, we found three patients had Stage I disease, 7 had Stage II, 13 had Stage III, and 23 had Stage IV disease. On correlating age with disease stage in our patients, we found that 11/19 patients (57.9%) < 3 years compared to 25/27 patients (92.6 %) > 3 years had advanced disease indicating that an increase in patient's age is associated with advanced stage of NBL [Table 2].

In our study, all children with unilateral abdominal NBL were reviewed and also investigate the five children with rare presentations separately to have a better understanding of their disease behavior as mentioned below.



Figure 2: Magnetic resonance imaging abdomen of Lt. adrenal neuroblastoma showing high-signal intensity tumor mass compared with the muscle on T2-weighted images. The lower medial part of the mass is heterogeneous, reflecting degeneration or necrosis

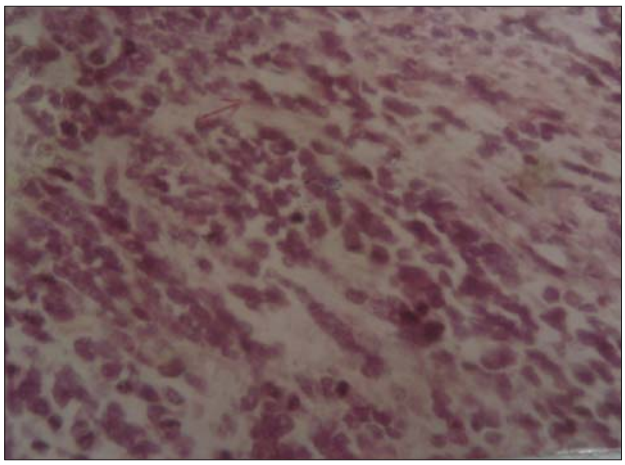


Figure 3: Microscopic picture of a case of neuroblastoma showing masses of small round and oval cells (neuroblasts) and Schwannian stroma in-between. The cells also showed characteristic resetting appearance (arrow) (H and E, ×4)

Table 2: Correlation between age and disease stage in 46 neuroblastoma patients

Age	Stage				Total no.	%
	I	II	III	IV		
<3 years	2	6	5	6	19	41.3
>3 years	1	1	8	17	27	58.7
Total no. (%)	3 (6.5)	7 (15.2)	13 (28.3)	23 (50)	46 (100)	100

36 (78.3%) of all 46 patients had advanced disease (Stages III and IV) at the time of diagnosis and 11/19 patients (57.9%) <3 years compared to 25/27 patients (92.6 %) >3 years had advanced disease and 6/19 patients (31.6%) <3 years compared to 17/27 (63 %) >3 years had metastatic disease indicating that an increase in patient's age is associated with advanced stage of neuroblastoma

Three- and six-year old boys each presented with a left hypochondrial mass. US and CT showed a well-circumscribed mass with central hemorrhage and necrosis at the site of left suprarenal gland compressing the left kidney and displacing it downwards [Figure 4a]. Exploration revealed a large rounded mass, safely dissected from tail of pancreas, spleen, and Lt. kidney [Figure 4b]. They were removed, histopathologically examined, and proved to be Stage I ganglioneuroblastoma [Figure 4c] with favorable shimada histology in one patient and did not receive adjuvant chemotherapy, whereas the other patient had unfavorable histology and received adjuvant chemotherapy [Table 3] with good disease-free survival in both patients.

Eighteen-month-old female child presented with recurrent attacks of urine retention and frequent catheterization. US, 1VU, and CT showed a well-defined oval-shaped heterogeneous mass 4.7 cm × 4 cm postero-lateral to urinary bladder [Figure 5]. Exploration and complete surgical removal of the tumor through a supra-pubic incision were done and histopathologically proved to be Stage I favorable histology pelvic NBL, accordingly the child did not receive adjuvant chemotherapy [Table 3] with a good disease-free survival during all the period of follow-up.

A 6.5-year-old male child presented with a very large left-sided abdominal mass extending into the pelvis and crossing the mid-line together with limping. CT and IVU showed a huge heterogeneous left pelviabdominal mass adherent to surroundings and compressing and displacing the urinary bladder to the right side [Figure 6]. CT-guided biopsy was taken, histologically examined, and proved to be pelviabdominal NBL. The patient received induction chemotherapy with no response of the tumor. Later on, the child developed paraplegia and ^{99m}Technitium bone scan showed metastases in mid-dorsal vertebrae, skull, ribs, both humeri, and both femurs. The patient was also given palliative radiotherapy plus dose intensive chemotherapy [Table 3].

A 2-year-old female child presented with abdominal enlargement, recurrent abdominal pain, and a palpable right hypochondrial mass. US showed multiple abdominal masses of same echogenicity related to both kidneys and in right hypochondrium. Contrast CT showed multifocal primary tumor (right suprarenal mass

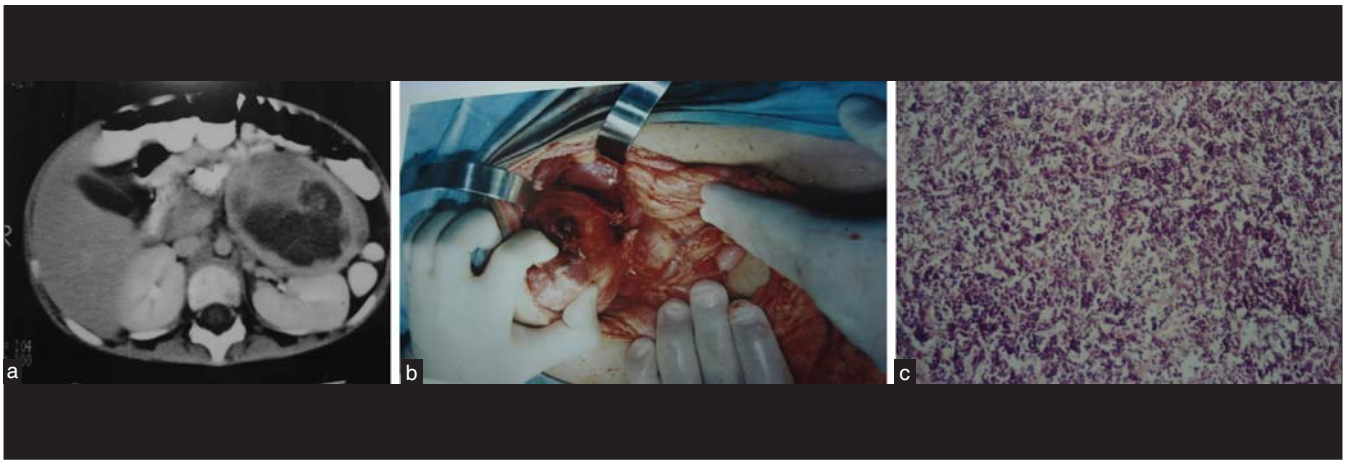


Figure 4: (a) Computed tomography abdomen of Lt. adrenal ganglioneuroblastoma showing a well-circumscribed heterogeneous mass with central hage and necrosis compressing the Lt. kidney and displacing it downwards (flower drop appearance). (b) Operative photography of the same case of ganglioneuroblastoma showing the tumor mass after its dissection from spleen (upper arrow) and Lt. kidney (lateral arrow). (c) Microscopic picture of the same case of ganglioneuroblastoma showing sheets of small rounded cells (neuroblasts) admixed with mature ganglion cells with Schwannian stroma in-between (H and E, ×125)

Table 3: Treatment modalities in five rare cases of abdominal neuroblastoma

Surgery	Stage				Total no.	%
	I	II	III	IV		
Surgical excision only	2	–	–	–	2	4.3
Surgical excision+chemotherapy	1	–	–	1	1	2.1
Biopsy+chemotherapy	–	–	–	1	1	2.1
Biopsy+chemotherapy+radiotherapy	–	–	–	–	1	2.1
Total	3	–	–	2	5	10.7

Complete surgical removal of the tumor could be done in pelvic and ganglioneuroblastoma (three patients) and only tissue biopsy in pelviabdominal and bilateral Neuroblastoma (NBL). All patients received adjuvant chemotherapy±radiotherapy except pelvic NBL and favorable histology GNBL

infiltrating Rt. kidney, left suprarenal mass infiltrating Lt. kidney, Rt. hypochondrial mass) and two similar mid-line masses [Figure 7a]. IVU showed the functioning of both kidneys. CT-guided biopsies of masses were done and proved histologically to be bilateral adrenal NBL. Induction chemotherapy was started with good initial response after the 3rd cycle of chemotherapy [Figure 7b] followed by relapse and development of metastatic subcutaneous nodules (in scalp and anterior abdominal wall) and also hemorrhagic pleural effusion. The nodules were biopsied and effusion was aspirated; histologically examined and found containing neuroblasts. Pleurodesis was done after drainage of effusion and the patient shifted to dose intensive chemotherapy regimen [Table 3] but he deteriorated later on and died from progression of disease and burden of chemotherapy.

For the 41 patients with unilateral abdominal NBL, the primary tumor was found resectable at the time of diagnosis in 12 patients and primary surgical excision of tumor could be done followed by post-operative chemotherapy with or without radiotherapy according to their disease Stages (II, III, IV). In the remaining 29 patients, the primary tumor was found unresectable or advanced for safe primary surgical removal; so, guided or laparoscopic biopsies were taken and the patients received induction chemotherapy with marked reduction in the size of the tumor (good response) in seven patients who underwent safe delayed surgical excision of tumor, whereas in the other 22 patients, the tumor showed no response to chemotherapy and the patients given palliative chemotherapy with or without radiotherapy according to their disease Stages (III and IV) [Table 4].

All our patients received post-operative (adjuvant) chemotherapy except two patients with Stage I disease

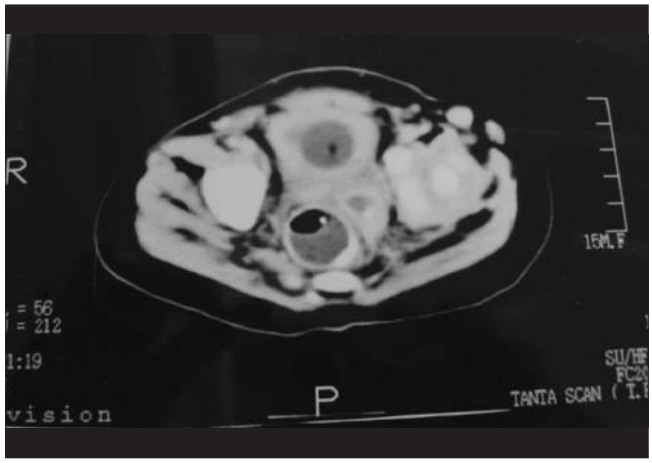


Figure 5: Computed tomography of pelvic neuroblastoma showing an oval heterogeneous mass 4.7 cm × 4 cm postero-lateral to the urinary bladder

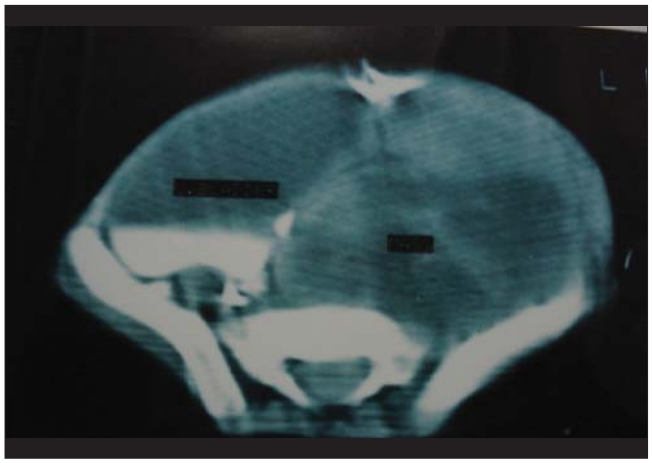


Figure 6: Computed tomography of Lt. pelviabdominal neuroblastoma showing a huge heterogeneous pelviabdominal mass compressing and completely displacing urinary bladder to the Rt. side

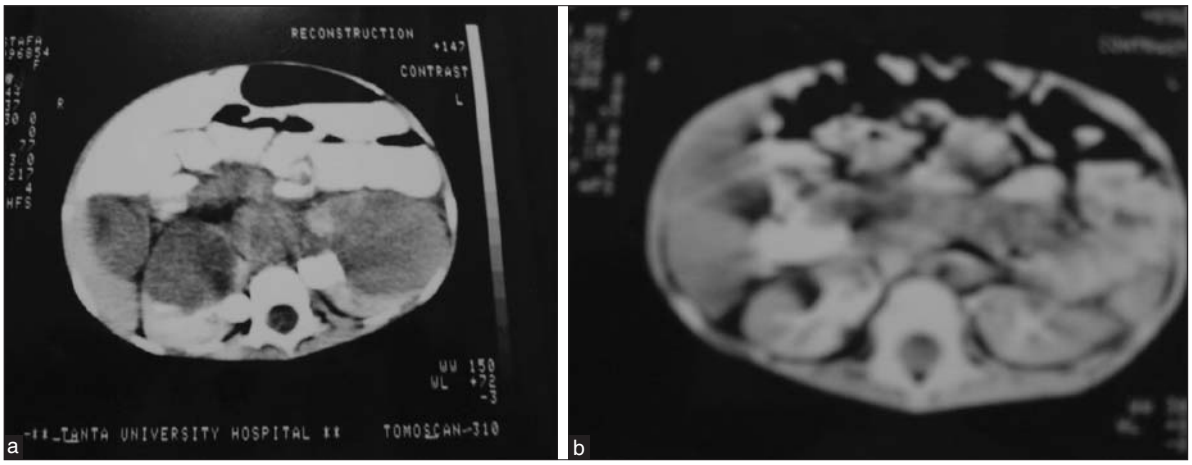


Figure 7: (a) Computed tomography abdomen of bilateral neuroblastoma (before chemotherapy) showing multifocal primary tumor (right suprarenal mass infiltrating Rt. kidney, left suprarenal mass infiltrating Lt. kidney, Rt. hypochondrial mass and two similar mid-line masses (? LNs involvement). (b) Computed tomography abdomen of the same case (after chemotherapy) showing partial response to chemotherapy and reduction in size of all tumor masses

Table 4: Different treatment modalities in 46 neuroblastoma patients

Stage	Surgery			Chemotherapy	Radiotherapy
	Primary surgical removal	Delayed surgical removal	Biopsy		
Stage I	3	-	-	1	-
Stage II	7	-	-	7	-
Stage III	4	4	5	5	8
Stage IV	1	3	19	18	5
Total	15	7	24	31	13
%	32.6	15.2	52.2	67.4	28.3

Out of 46 patients, primary or delayed surgical excision of tumor could be done in 22 (47.8%), patients, whereas in 24 (52.2%) patients with advanced tumors, only tissue biopsies were taken as they did not respond to induction chemotherapy. All patients received adjuvant chemotherapy±radiotherapy except two patients with Stage I favorable histology

(pelvic NBL and favorable (ganglioneuroblastoma) GNBL), whereas pre-operative (neoadjuvant) chemotherapy given for 31 patients with advanced disease (including pelviabdominal and bilateral NBLs). The chemotherapeutic regimen used in our patients was OPEC/OJEC regimen which consists of OPEC (oncovin, cisplatin, etoposide, and cyclophosphamide) for courses one, three, and five and OJEC (oncovin, carboplatin, etoposide, and cyclophosphamide) for courses two, four, and six. Sometimes, dose intensive regimen was used in high-risk patients or those not responded to the previous regimen; it consists of vincristine, cyclophosphamide, and doxorubicin for courses one, two, and four, and etoposide and carboplatin for courses three and five. Post-operative external beam radiotherapy was added to adjuvant chemotherapy in high-risk tumors and those spread to several parts of the body.

All patients were followed up during all period of study with a median follow-up period of 24 months (range: 6-48) with overall survival rates of 100%, 85.7%, 30.8%, and 8.7% for Stages I, II, III, and IV, respectively.

DISCUSSION

NBL is a tumor primarily of infants and younger children originating from sympathetic neuroblasts. The tumor location, growth, and biologic behavior represent its clinical manifestations: It ranges from spontaneous regression up to eminently malignant development with resistance to any therapy. Miscellaneous markers and imaging techniques with varying validity are available. The prognosis for most patients, especially the older ones with metastatic disease remains poor.[8]

Castleberry correlated the age with disease stage in NBL patients and found that the incidence of metastatic disease in older children is higher (68%) than that of localized disease (19%).[9] Koh *et al*. found that 59.1% of their patients have metastasis at diagnosis.[10] In our patients, 78.3% had advanced disease (Stages III and IV) at diagnosis and on correlating age with the disease stage, we found that 57.9% of patients <3 years compared to (92.6 %) > 3 years had advanced disease indicating that an increase in patient's age is associated with advanced stage of NBL.

Alexander found that nearly 35% of cases occur before 1 year of age, the median age at diagnosis is 2 years and male to female ratio is 1.25:1,[11] while in Ayden *et al*.'s study, the median age was 2.9 years and male/female ratio was 1.3/1.[12] In our patients with rare presentations, the mean age was 4.5 years and male to female was 3:2, while in those with conventional unilateral abdominal NBL, the mean age was 3.9 years and male to female ratio 1.3:1.

In Kitonyi *et al*.'s study, the commonest presenting features of NBL were abdominal swelling (53.8%), inability to walk due to bone pains (50%), anemia (72.7%), and periorbital swelling (38.5%),[13] while in Massed series, the abdominal mass presented in 99.6% of cases, it arise from the adrenal gland in 34 cases (60.7%) and from the sympathetic chain in 22 cases (39. 3%).[14] All our patients presented with abdominal mass (pelviabdominal in one) except one patient with pelvic NBL presented with recurrent attacks of urine retention (2.2%), other manifestations associated with the tumor mass are shown in Table 1.

In this study, urinary VMA was elevated in 82.6% of patients and serum NSE in 91.3%, whereas BM was infiltrated by neuroblasts in 38.9% of tested children. Smith *et al*. stated that, although elevated urinary catecholamine levels have been reported in 90-95% of neuroblastoma patients, some patients have reported normal values at time of presentation regardless the disease stage.[15] Sharp found that urinary VMA was elevated in 63% of the tested children and 60% of patients have metastatic disease.[16] Berthold *et al*. found that NSE level has increased with the disease stage and not influenced by histologic differentiation,

its specificity was 91.3%, sensitivity 73.0% and proved to be a reliable tumor marker for monitoring of NBL.[17]

In this study, we reported two patients (4.3%) out of 46 had ganglioneuroblastoma Stage I disease with favorable histology in one patient and unfavorable histology in the other. The tumor completely excised with good outcome in both patients. Nakaoka *et al*., reported a rare case of retroperitoneal GNBL Stage I, unfavorable histology arise from the sympathetic trunk and resected 8 years after mass screening.[18] In Ayden *et al*.'s study, the incidence of GNBL among NBL patients was 7.6%.[12] Angelini *et al*. concluded that patients with GNBL are rare (5.6% in his study), older (83% > 18 months), and have heterogeneous outcome according to their histology.[19]

We reported a rare case of pelvic NBL presented with recurrent attacks of urine retention with frequent catheterization, completely excised primarily with a good disease-free survival. Rasmussen reported a 9-month infant presented with the same complaint of recurrent attacks of urine retention. By per-rectal examination (PR), US, and CT, he discovered a soft tissue mass in the pelvis that was excised and pathologically confirmed to be pelvic NBL.[20] Mills *et al*. also reported a rare case of retroperitoneal NBL causing urinary obstruction in a 5-month-old boy.[21] Hasse *et al*., in his study, found that the 3-year disease-free survival for pelvic NBL was 70% compared to 47% for non-pelvic NBL ($P = 0.04$) and concluded that pelvis is an unusual primary site for NBL but represents a more favorable prognostic factor in improving survival to be better than non-pelvic tumors because children with pelvic tumors have some favorable biological factors than those with non-pelvic tumors.[22]

We also reported a rare case of bilateral adrenal NBL, received pre-operative chemotherapy with good initial response followed by relapse and development of metastatic subcutaneous nodules and hemorrhagic pleural effusion but we did not test our patient for gene amplification as we did not have this facility in our institutions. Pederiva *et al*. identified four cases of bilateral NBL among 148 patients with unilateral NBL reviewed between 1992 and 2006, three had subcutaneous nodules. All underwent chemotherapy prior to surgery, two infants had gene amplification and died of widespread metastases some weeks after bilateral adrenalectomy. The other two children were not amplified and did well after unilateral adrenalectomy. He concluded that bilateral NBL is an extremely rare tumor and can be due to multifocal primary or contralateral metastasis and staging is confusing. It has an exceptional behavior, variable *N myc* amplification, widespread metastases, and a high mortality, so it requires individually tailored therapeutic strategies based on size, extent of tumor, and prognostic markers.[23] Brankov *et al*. found that five cases (2.6%) had multifocal lesion among NBL children reviewed between 1979 and 2005, all were treated successfully with surgery, chemotherapy, and one received radiotherapy with good disease-free survival rates.[24] Pages *et al*. also reviewed 15 cases with bilateral NBL treated between 1988 and 2004 by French Society of Pediatric Oncology, compared to the 45 cases reported in literatures and showed good overall survivals concluding that the majority of bilateral NBL carry a favorable prognosis except those exhibiting risk factors, such as *N myc* amplification.[25]

In our study, 31 patients with advanced NBLs including pelviabdominal and bilateral NBL received pre-operative chemotherapy with good response in seven children who underwent safe delayed surgical removal of the tumor, partial response in bilateral NBL followed by relapse, and no response in 23 patients. Shamperger *et al*., in a comparative study between primary and delayed surgical resection of tumor of 60 patients with advanced NBL, concluded that delayed surgical resection of advanced NBL is safer after initial chemotherapy but with no difference in the overall survival rate.[26] Haase *et al*. concluded that advanced NBL resection is facilitated by induction chemotherapy and delayed surgery may be effective in improving the patient outcome whenever the metastatic foci have been controlled.[22]

Our study included 3 Stage I (6.5%) patients, 7 Stage II (15.2%), 13 Stage III (28.2%), and 23 Stage IV (50%) patients. Primary complete surgical removal of tumor could be done in 15 patients, delayed excision in seven, and only tissue biopsy in 24 patients. All patients received post-operative chemotherapy with or without radiotherapy except two children with overall survival rates of 100%, 85.7%, 30.8%, and 8.7% for Stages I, II, III, and IV, respectively. In Massad *et al*.'s study, 3.8% patients were Stage I, 15% Stage II, 15% Stage III, and 55% Stage IV. Seventeen patients underwent total excision of the tumor, 14 partial excision, and 33 patients underwent tissue biopsy only. All cases received chemotherapy ± radiotherapy with 33.3% overall 2-year survival rate.[14] In Hesseling *et al*.'s study, 2% of patients had Stage I disease, 19% Stage II, 21% Stage III, and 50% Stage IV treated by total (13%) or partial (44%) resection of tumor after chemotherapy with overall survival rates of 90% for Stages I and II (combined), 51% for Stage III, and 6%

for Stage IV after 5-163 months' follow-up.[27] Fayea *et al*. reviewed 52 children with NBL > 1 year and found six patients (11%) had Stage II, 12 (23%) Stage III, and 34 (65%) Stage IV. Three patients of Stage II disease treated with surgery only, whereas all patients of Stages III and IV treated with induction chemotherapy and surgery ± RT. The 2-year overall survival rates were 100%, 83%, and 12% for Stages II, III, and IV, respectively.[28] Aydn *et al*. found that 6% of his patients had Stage I, 9.8% had Stage II, 26.6% had Stage III, and 51.4% had Stage IV disease. They were treated with surgery and chemotherapy ± radiotherapy with 10-year overall survival rates of 100%, 75.8%, 34.1%, and 6.5%, respectively.[12] We can notice that, the overall outcome of NBL in our patients and in the above-mentioned studies is still not encouraging even with skillful use of combined surgery and chemoradiotherapy because at least 50% of patients presented with advanced disease at the time of diagnosis.

From this study, we can conclude that primary complete surgical removal of tumor is advisable in localized NBL with a good outcome, whereas in advanced cases, it is better to start with pre-operative chemotherapy for downsizing of tumor mass and safe delayed surgical excision. An increase in patient's age is associated with advanced stage of NBL and poor prognosis except in ganglioneuroblastoma cases due to maturation of tumor cells. Among our patients with unilateral abdominal NBL, 10.7% of patients could present with a rare presentation. It had a good outcome in patients with ganglioneuroblastoma and pelvic presentation, while in those with pelviabdominal and bilateral presentation, the prognosis was poor.

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