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Case report

Cystic poorly differentiated nephroblastoma: A case report and review of literature



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Abstract

Background: Cystic poorly differentiated nephroblastoma (CPDN) is a rare variant of nephroblastoma which follows a benign clinical course.

Case diagnosis/treatment: In this report, we document a case of CPDN in a 2 year old boy who presented with recurrent gross painless hematuria and progressive abdominal distension. Abdominal ultrasound showed a multicystic lesion and CT scan features of Stage III Wilms tumour. Nephrectomy was done after two cycles of chemotherapy according to the SIOP Nephroblastoma therapeutic protocols. Histology showed blastemal cells in the wall of only one of the cysts, with no solid expansile nodules. The patient had to have five more cycles of chemotherapy and also radiotherapy for residual tumour.

Conclusions: Surgery is curative in Stage I CPDN and adjuvant therapy is not required. Adequate sampling is critical to ensure accurate diagnosis and appropriate management. We suggest that a minimum of 2–3 tissue sections should be taken per centimetre of tumour diameter. Related entities including cystic nephroma, cystic Wilms tumour and completely necrotic nephroblastoma are discussed in the differential diagnosis.

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Introduction

Cystic poorly differentiated nephroblastoma (CPDN) is a rare variant of nephroblastoma [1]. To the best of our knowledge, this is

the first documented case of this variant of nephroblastoma from Nigeria.

Cystic poorly differentiated nephroblastoma is a multilocular cystic variant of Wilms tumour which follows a benign clinical course [1,2]. Surgery is curative in almost all patients [1–3]; and the rare cases of local recurrence are thought to be due to incomplete resection [1,2,4]. Patients with Stage I CPDN can appropriately be managed by nephrectomy and conservative follow-up alone, with no adjuvant therapy indicated [1–4]. Once tumour does not extend beyond the kidney, tumour does not involve the resection

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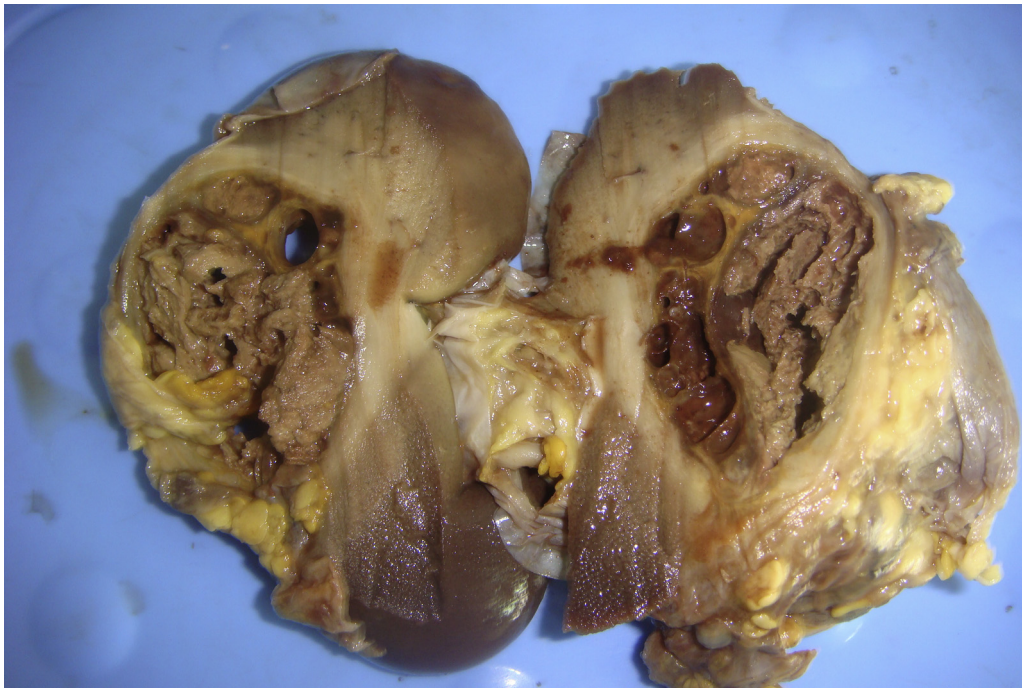


Figure 1 Macroscopic picture of the kidney with a multicystic lesion at the midportion and residual kidney tissue at both poles.

margins, and tumour spillage does not occur during nephrectomy, surgery alone would be curative in a patient with CPDN [1–4]. Hence, it is pertinent that the patients presenting with CPDN are accurately diagnosed and are not managed like high risk nephroblastoma. This will ensure that patients with nephroblastoma are spared from the administration of adjuvant therapy in all clinical situations where it may be unnecessary and potentially harmful [5,6].

Case diagnosis/treatment

We present a 2-year-old boy who was first seen at the Children's Emergency ward having been referred from a private hospital on account of hematuria, an abdominal ultrasound which was said to have been suggestive of the left polycystic kidney, and intravenous urogram suggestive of the left cystic nephroma.

The patient had had hematuria on and off for 4 weeks prior to presentation. During each episode, the passage of blood was total and painless. At presentation, he also had progressive abdominal distension of 8 days' duration and high grade continuous fever of 5 days' duration. There was significant background history of failure to thrive.

On examination, he was found to have high grade fever and a left flank mass measuring 5 by 6 cm. Full blood count showed a packed cell volume (PCV) of 23% and differential white blood cell count showed 60% neutrophilia, both likely due to sepsis. The erythrocyte sedimentation rate (ESR) was moderately elevated. Urine microscopy showed features suggestive of urinary tract infection. An assessment of possible nephroblastoma with sepsis, with the focus in the urinary tract was made. Abdominal ultrasound showed multiple cysts with extensive areas of necrosis but no solid areas,

these features were said to be suggestive of a cystic Wilms tumour. Abdominal CT scan showed features consistent with nephroblastoma Stage III.

A radical nephrectomy was performed after 2 courses of chemotherapy with vincristin, actinomycin D and doxorubicin. There had been no prior pre-chemotherapy biopsy or diagnosis. At surgery, the renal tumour was found to have infiltrated the muscles of the posterior abdominal wall (SIOP Stage III disease).

Gross examination showed a kidney weighing 150 g and measuring 9 cm × 7 cm × 3 cm. There was infiltration of the renal capsule by tumour with extension into the perinephric fat. There were no enlarged lymph nodes within the perinephric fat. The adrenal gland was not involved by the tumour.

Cut sections through the left kidney showed a lesion located about the mid-portion of the kidney with residual renal tissue at both poles; it measured 5 cm × 4 cm × 2.5 cm. The lesion was totally cystic with no solid areas identified. Some of the cysts contained chocolate-coloured or serous fluid, others of gelatinous material and a single cyst consisted entirely of yellowish-brown necrotic material (Fig. 1).

Histology showed a well circumscribed lesion consisting of multiple cysts which did not communicate with one another or with the renal pelvis. These cysts were lined by cuboidal to columnar epithelium which appeared attenuated or absent in some of the cysts. Some are lined by cells with a hobnail appearance. The cysts are separated by delicate fibrous septa. Old and recent hemorrhage were seen within the lumina of some of the cysts. Sheets of foamy macrophages, hemosiderin-laden macrophages admixed with lymphocytes and plasma cells are seen within the walls of many of the cysts. One of the cysts shows necrotic debris within its lumen. Blastemal cells

are seen within the wall of another of the cysts. There were no associated immature stromal or epithelial elements. There were no solid expansile nodules. The round contour of the cyst with blastemal cells in its wall is maintained and is not distorted by the cell clusters. No areas of anaplasia are seen. There was no involvement of the hilar vessels by tumour. The ureter appeared unremarkable.

Since surgery, the patient has had five more courses of chemotherapy and external beam radiotherapy to the tumour bed. The patient developed pancytopenia after chemotherapy which was managed with supportive therapy consisting of transfusions with blood and platelet concentrate. There were recurrent episodes of sepsis delaying the commencement of a new cycle of chemotherapy on two occasions.

Treatment was completed in April 2012, and the post-treatment course has been uneventful.

Discussion

Cystic poorly/partially differentiated nephroblastoma is a multilocular cystic variant of Wilms tumour composed entirely of cysts lined by flattened to cuboidal epithelium and separated by delicate septa [1–4]. The septal stroma contains small foci of blastema, primitive or immature epithelium, and/or immature appearing stromal cells, and this feature distinguishes CPDN from cystic nephroma [1–4].

Cystic nephroma and CPDN are histologically distinct but grossly and radiologically identical. In other words, these entities cannot be differentiated on imaging studies or on naked eye examination of the kidney [1,7,8]. Cystic nephroma is sometimes classified with cystic partially differentiated nephroblastoma (CPDN) as a multilocular cystic renal tumour [8]. In 1989, Joshi and Beckwith proposed modified terminology and refined diagnostic criteria to help differentiate cystic nephroma from CPDN and other cystic renal tumours such as Wilms tumour with cyst formation [7,9].

Virtually all cases of CPDN are diagnosed in children younger than 24 months [1–3], and males are affected about twice as often as females [1,2]. The index patient, a 2-year-old boy falls within the peak age range of occurrence for CPDN.

He presented with hematuria, a less common symptom of nephroblastoma than abdominal mass which is the most common presenting feature [1,3]. A flank mass was found on clinical examination.

A clinical diagnosis of nephroblastoma had been made in this patient based on the clinical history, findings on clinical examination and radiologic findings. CPDN is often diagnosed as Wilms' tumour on clinical and radiologic grounds [3].

For pediatric tumours, a minimum of one section for each centimetre of the diameter of the tumour is recommended during sampling for histology [10]. This would suggest that obtaining a minimum of five sections in the index patient, whose kidney tumour had a widest diameter of 5 cm, should have been adequate. We initially reviewed eight sections which were obtained from various areas of the lesion after bivalving and serial sectioning. None of these sections showed nephroblastoma cells in the walls of the cysts and a diagnosis of cystic nephroma would have been submitted with significant clinical implications.

The CT and intraoperative findings in this patient had, however, appropriately led the pathologist to also consider the possibility of a CPDN or cystic Wilms tumour in this multilocular cystic lesion of the kidney. Consequently, further sections were obtained. One of the six additional sections showed blastemal cells in the wall of only one of the cysts seen. We suggest that for multicystic tumours of the kidney in children, the criteria for adequate sampling should be extended such that a minimum of two to three sections is obtained per centimetre of the diameter of the tumour. Further studies would help to clearly define specific adequate sampling criteria for multicystic tumours of the kidney.

Widespread sampling of multiple cyst walls with special attention to the areas where the walls are not transparent will significantly increase the possibility of finding the diagnostic nephroblastoma cells—blastemal cells, epithelial and or stromal elements.

The results of the International Society of Paediatric Oncology (SIOP) trials and studies published in 2002 highlight the important role that the finding of blastemal cells in nephroblastoma plays in prescribing prognosis to patients [11]. They showed that, for treatment purposes, only three major types of nephroblastoma need to be recognized: completely necrotic (low risk tumour), blastemal (high risk tumour), and others (intermediate risk tumours).

This patient was managed using the SIOP therapeutic protocols which recommend pre-operative chemotherapy. The main advantage of this treatment protocol is that it significantly reduces the likelihood of tumour spillage during nephrectomy [12]. The National Wilms Tumor Study (NWTS) therapeutic protocol requires that nephrectomy is done immediately and a diagnosis is made before treatment is commenced, with the advantage of ensuring that chemotherapy is not administered in error to a patient with benign disease or a different histological type of malignant tumour [12]. Overall, it has been shown that the SIOP and NWTS therapeutic protocols both yield almost equivalent clinical outcomes [12].

During nephrectomy, this patient was found to have Stage III disease with local infiltration of tumour into the capsule, perinephric fat and the muscles of the posterior abdominal wall. This necessitated the administration of additional cycles of chemotherapy after surgery and the application of radiation to the tumour bed. It is known that even though all cases of CPDN are associated with a relatively good prognosis, adjuvant therapy has to be offered to patients with more advanced disease than Stage I to ensure favourable outcomes. A study of the response to treatment of children with CPDN who were recruited into the NWTS showed favourable outcomes in these patients with 100% survival rate and no recurrences. For Stage I disease, these outcomes were achieved with or without chemotherapy but Stage II and more advanced disease required addition of chemotherapy to obtain favourable outcomes [13].

In this patient, microscopic examination showed an entirely cystic lesion with blastemal cells found within the wall of one of the cysts (Fig. 2). No immature stromal or epithelial elements were seen within the fibrous septa separating the cysts. A confounding fact is whether to strictly refer to a renal tumour such as is found in this patient as a cystic poorly differentiated nephroblastoma because it consists of blastemal cells alone and a tumour with blastema along with more differentiated tissue including

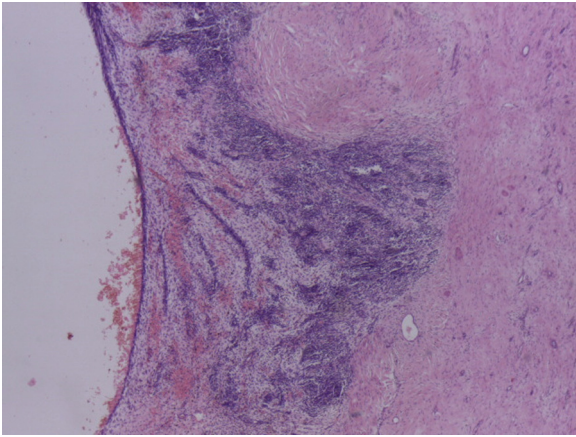


Figure 2 A photomicrograph showing a cyst with blastemal cells within its wall (x40).

epithelial and mesenchymal elements as a cystic partially differentiated nephroblastoma. Notably, Joshi showed that available data do not suggest any difference in clinical behavior between the two [3]. Moreover, there is a suggestion that there might be two subtypes of cystic partially differentiated nephroblastoma—one with predominantly well-differentiated elements and the other with predominantly poorly differentiated elements—but no definite conclusions can be drawn regarding the existence of such subtypes on the basis of available data [9].

Hemorrhage and necrosis were found in this patient's renal tumour. In Wilms tumour, extensive necrosis is known to occur following chemotherapy. When no viable tumour is left after pre-nephrectomy chemotherapy, the diagnosis of a completely necrotic nephroblastoma is most appropriate. This is defined as a unilateral non-anaplastic nephroblastoma showing total necrosis and no viable tumour following preoperative chemotherapy [6]. This is a low risk variant of nephroblastoma. In the index patient, abdominal ultrasound had shown a multicystic renal lesion with extensive necrosis and no solid areas even before chemotherapy was commenced, on the day after presentation to LUTH.

Other post-chemotherapy changes that are known to occur in a nephroblastoma include xanthomatous histiocytic foci, hemosiderin deposits and fibrosis. Chemotherapy may also induce changes such as maturation of blastema, epithelial, and stromal components, with striated muscle being the most frequent component seen [14].

Hemorrhage and necrosis are both known to be uncommon in multilocular cystic renal tumours [3,7,9], but focal hemorrhage and necrosis may occur following herniation of the tumour into the renal pelvis or ureter, which damages the thin layer of transitional epithelium [7].

Cystic degeneration is known to occur in Wilms tumour following hemorrhage and necrosis into the tumour with loss of tissue [8].

Wilms' tumour with multifocal cystic change has to be distinguished from CPDN [1,9]. The diagnosis of a cystic Wilms tumour is rendered when solid expansile nodules are identified even in the presence of extensive areas of cystic degeneration in a nephroblastoma [1].

The report of the International Society of Paediatric Oncology (SIOP) nephroblastoma trial and study 9, published in 2000 [6] observed that the high cure rates achieved for nephroblastoma in the SIOP Nephroblastoma Trials and Studies has led to increased attention to the identification of low risk variants of nephroblastoma and of patients who could benefit from less aggressive postoperative therapy. Even from the outset, the identification of low-risk groups has been one of the aims of the SIOP Nephroblastoma Trials and Studies [6].

In Nigeria, such high cure rates have not yet been achieved in nephroblastoma seen in many of the tertiary hospitals [15,16] but a focus on variants of nephroblastoma requiring less aggressive therapy is just as useful to save our mostly indigent patients the costs of chemotherapy and radiotherapy when such treatment modalities offer no additional advantage, and to avoid the morbidity and the late effects of adjuvant therapy.

Challenges preventing a huge success in the management of nephroblastoma in Nigeria include late presentation with advanced disease, reduced health awareness and poverty [15–17]. These factors make it difficult for high cure rates to be achieved.

A more recent article [18] described similar challenges in the management of malignant solid tumours in sub-Saharan Africa. These include resource deficiencies that range from inadequate healthcare budgets and a paucity of appropriately trained personnel, to scarce laboratory facilities and inconsistent drug supplies [18]. Patients face difficulties accessing healthcare, they often cannot afford to pay for investigations and or treatment protocols, or to attend routine clinic follow-up visits [18]. Children routinely present with advanced local and metastatic disease hence many children cannot be offered any effective treatment [18]. In addition, multiple comorbidities, including malaria, tuberculosis and HIV, when added to acute or chronic malnutrition, tend to compound treatment-related toxicities [18]. The index patient had a history of failure to thrive and he presented with sepsis as co-morbidity. During chemotherapy, he had a recurrence of sepsis on two occasions which delayed the next cycle of treatment by at least one week on each occasion. Overall, survival rates of patients with nephroblastoma in Africa are poor [18].

In conclusion, we have been able to illustrate that CPDN ought to be considered in children less than 5 years with a clinical diagnosis of nephroblastoma, and a multicystic lesion on imaging studies and on gross examination of the kidney. There is need for increased awareness about this entity among pathologists, paediatric surgeons and paediatricians to ensure that an accurate diagnosis can be rendered and the patient is appropriately managed.

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