OPEN ACCESS – CASE REPORT

Nephroblastoma in a 51-year-old Male: An Exceedingly Rare Occurrence of Malignant Embryonal Tumor in Adulthood

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ABSTRACT

Nephroblastoma is an uncommon renal malignancy primarily observed in the pediatric population, with its occurrence in adults being exceedingly infrequent. We describe an extremely rare case of a malignant embryonal tumor presenting in an adult patient with right renal mass. Final histopathologic diagnosis was nephroblastoma with favorable histology. Use of immunohistochemistry studies is generally unnecessary but its rarity in the adult population raises uncertainty in diagnosing this malignancy by histomorphology alone.

Key words: adult nephroblastoma, immunohistochemistry, Wilms tumor, kidney tumor

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INTRODUCTION

Wilms tumor or nephroblastoma is the most frequent renal malignant neoplasm in the pediatric population with a peak incidence between 2 and 5 years.[1] On the contrary, this is extremely rare in the adulthood accounting for less than 1% of all renal malignancies. Metastatic disease within diagnosis is more common in adults. Up to 50% of the cases are in the advanced stage (Stage III-V).[2] Establishing the diagnosis has been a great challenge for both clinicians and pathologists, who are not accustomed to considering nephroblastoma as a potential differential diagnosis in adults. Histomorphologic characteristics alone can be sufficient to confirm the diagnosis of nephroblastoma, particularly when the three distinct components—epithelial, blastemal, and stromal—are clearly identifiable. However, use of immunohistochemistry studies may be necessary to rule out other differential diagnoses especially if one or more components predominate than the others. Only less than 200 cases have been documented worldwide. Because of its rarity, standard management guidelines are not available for adult population and are solely based on the established treatment guidelines for pediatric patients by the International Society of Pediatric Oncology (SIOP).[3]

CASE

This is a 51-year-old male who presented with flank pain for 8 months associated with gross hematuria and gradually enlarging abdomen. Three months prior to admission, these symptoms persisted which prompted the patient to consult in a private clinic. CT urography was requested which revealed a right renal mass, predominantly endophytic, extending from the superior interporal region to the inferior pole, measuring at least 15.2 x 19.6 x 13.6 cm. The mass is well-circumscribed and does not invade the adjacent organs. The contralateral kidney and other organs such as urinary bladder, adrenal glands and para-aortic lymph nodes are unremarkable. Eventually, patient was referred to our institution for radical nephrectomy.

Patient is a known hypertensive and adherent to his maintenance medications. Pertinent physical examination findings include pale palpebral conjunctiva and tender mass

palpable in the right upper quadrant. Routine laboratory investigations including complete blood count, renal function tests and bleeding parameters were unremarkable except for the decreased red blood cell count, hemoglobin, and hematocrit, which denote anemia.

The specimen submitted for pathology consists of a single, intact, tan yellow to brown, soft to firm, smooth to rough right kidney weighing 2, 108 grams which measures19.5 x 16.0 x 14.0 cm. The attached ureter is grossly unremarkable which measures1.5 x 0.6 x 0.5 cm (Figure 1.) Serial sections of the right kidney show a well-delineated, tan cream to tan brown, complex, solid to cystic mass which measures 19.0 x 14.0 cm. The mass is predominantly solid with microcystic areas, areas of hemorrhage and extensive necrosis (80%). The mass is pushing the renal capsule but grossly uninvolved by the tumor (Figure 2).

Histopathologic examination of the right renal mass shows three distinct populations of tumor cells (Figure 3). One population represents the epithelial component of the tumor. These are in glandular or tubular architecture and rosette-like formation in a background of fibromyxoid stroma (Figures 4 and 5). The second population represents the blastemal component which consists of small blue round tumor cells in diffuse sheets. This is a highly cellular focus consisting of small to medium-sized undifferentiated cells with overlapping, relatively small, regular, and hyperchromatic nuclei with inconspicuous to visible nucleoli and scant cytoplasm (Figure 6). The third population consists of densely packed undifferentiated mesenchymal cells in fibroblastic stroma. These tumor cells

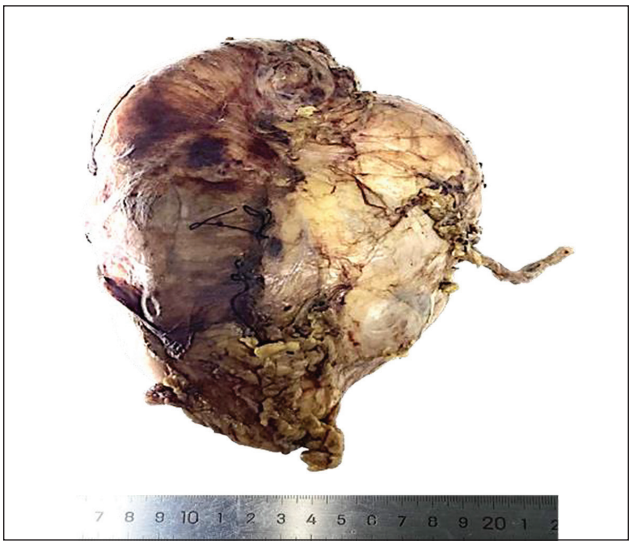

Figure 1. Gross appearance of the right kidney.

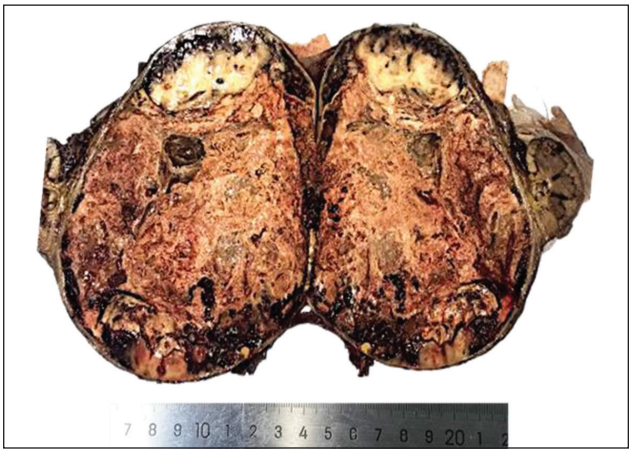

Figure 2. Cut section of the right kidney mass.

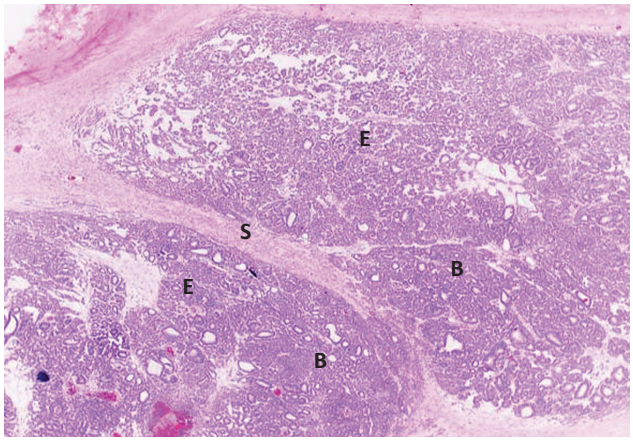

Figure 3. Triphasic tumor composed of epithelial **(E)**, blastemal **(B)** and stromal **(S)** components (H&E, 40x).

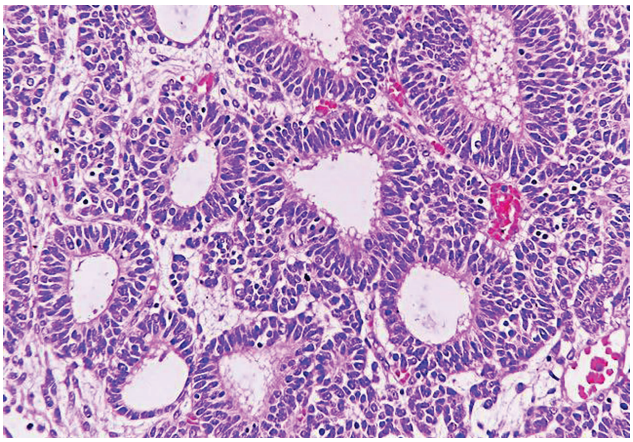

Figure 4. Epithelial elements composed of primitive tubular structures in a fibromyxoid stroma (H&E, 400x).

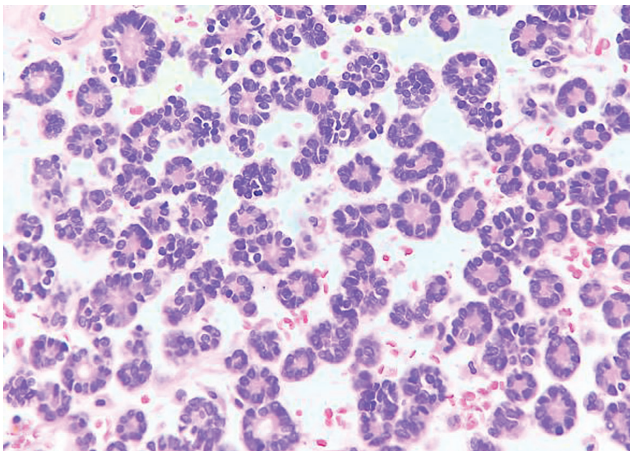

Figure 5. Epithelial component of the tumor in rosette-like formation (H&E, 400x).

have oval to spindle-shaped nuclei with bland nucleoli and indistinct cytoplasmic membrane (Figure 7). There are no areas with anaplasia. However, extensive necrosis and hemorrhagic areas are noted.

Histomorphologic features are very consistent with Nephroblastoma, but this is extremely rare in adult population. Due to its rarity, an accurate diagnosis requires careful exclusion of other potential differential diagnoses. The following are considered such as clear cell renal cell carcinoma with sarcomatoid differentiation, neuroblastoma, Ewing sarcoma, desmoplastic small round cell tumor, rhabdoid tumor, clear cell sarcoma, malignant germ cell tumor and metanephric adenoma. Despite the clear presence of the classic triphasic histologic features of nephroblastoma, immunohistochemistry studies were still done to support the diagnosis such as WT1, Vimentin, Pancytokeratin, Desmin, S100, CD34, Synaptophysin, SALL-4, CD99, CD10 and BCL2. CD10 is negative which rules out renal cell carcinoma. The positivity of WT1 and negativity of BCL2 rules out clear cell sarcoma. CD99 and synaptophysin are negative which rule out Ewing sarcoma and neuroblastoma, respectively. Negativity of Desmin and CD99 rule out rhabdoid tumor as well as desmoplastic round cell tumor. WT1 and vimentin positivity support the diagnosis of metanephric adenoma while BRAF and CD57 immunostains can help in excluding this differential diagnosis. However, it can be ruled out based on histomorphologic finding alone. Metanephric adenoma is a highly cellular tumor, characterized by its typical appearance of tightly packed small, and round to angulated acini and tubules.[4] The presence of the three components (epithelial, blastemal, and stromal), along with high mitotic activity and atypia, helps in excluding metanephric adenoma. Both epithelial and blastemal components are positive for WT1 (Figure 8). The epithelial component is positive for AE1/AE3. The stromal component is positive for Vimentin. Other immunostains such as Desmin, S100,

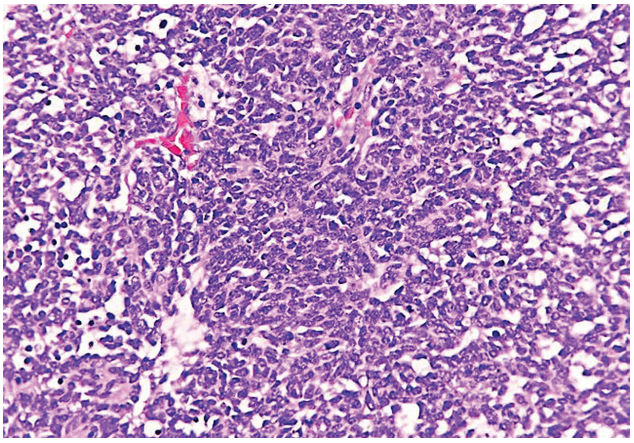

Figure 6. Blastemal component of the tumor arranged in diffuse sheets (H&E, 400x).

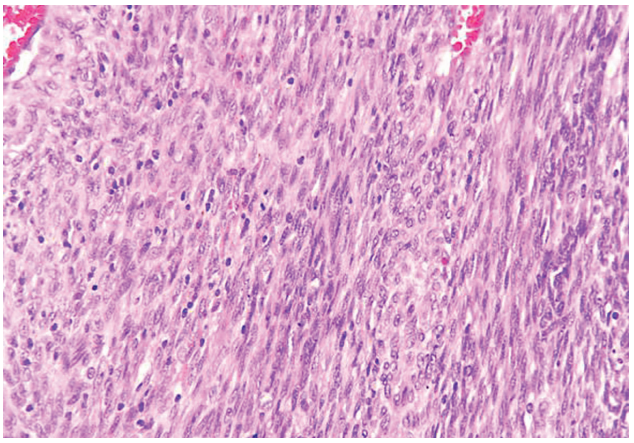

Figure 7. Stromal component composed of densely packed undifferentiated mesenchymal cells in fibroblastic stroma (H&E, 400x).

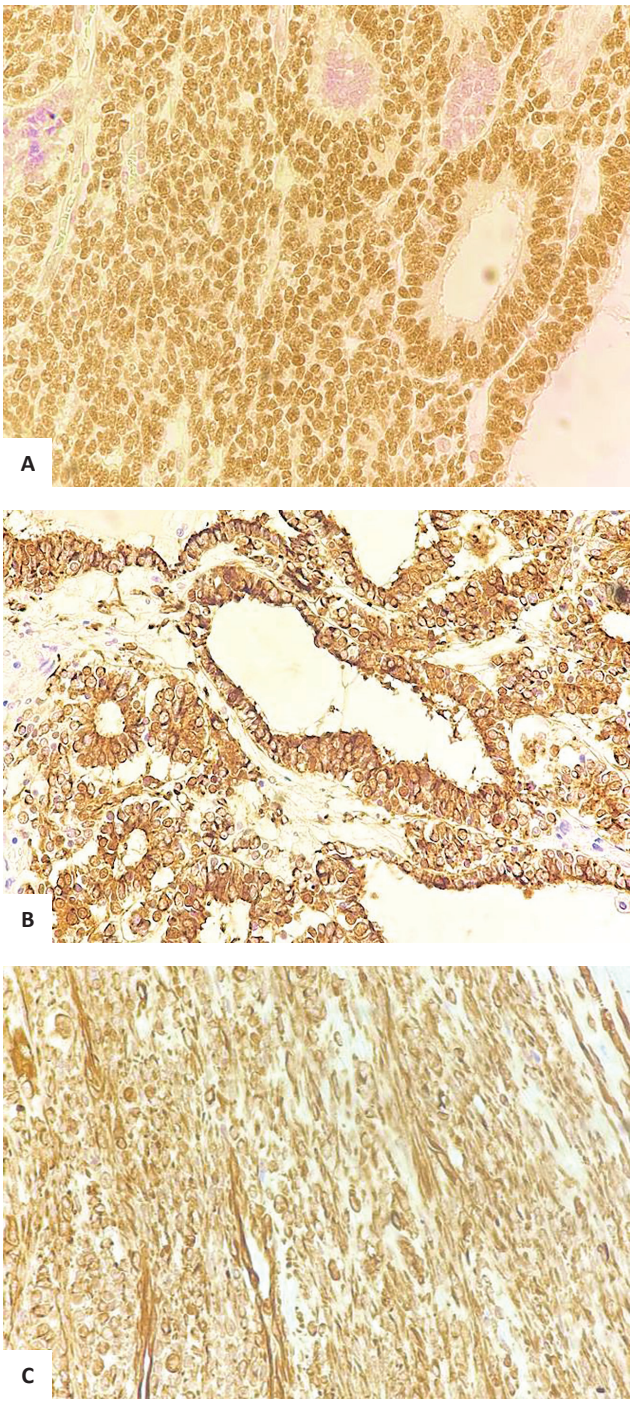

Figure 8. Immunohistochemistry showing: strong and diffuse, nuclear staining for WT1 **(A)**; strong and diffuse cytoplasmic staining for AE1/AE3 **(B)** and Vimentin **(C)**.

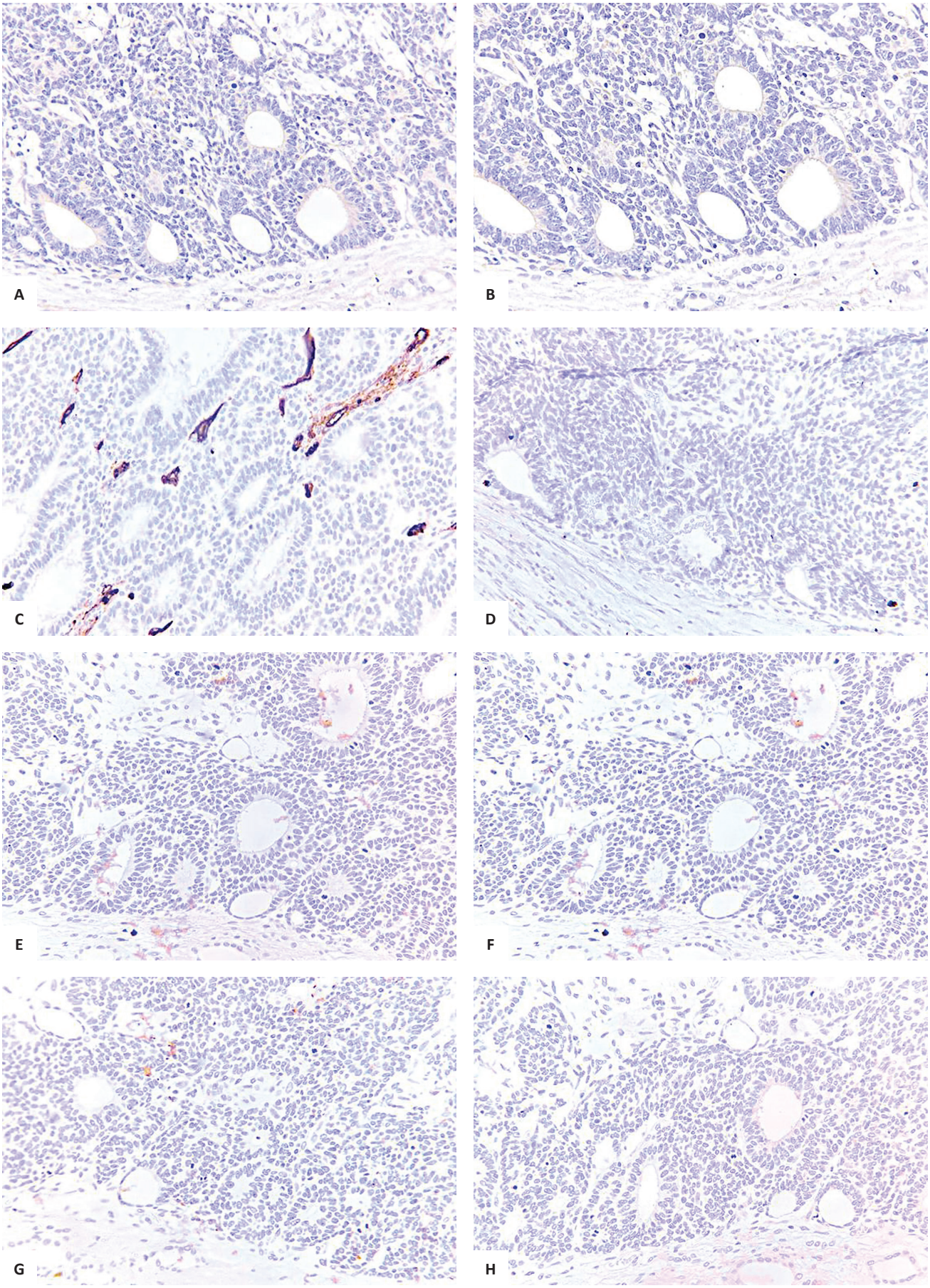

Figure 9. Negative immunohistochemical stains of the right renal mass: Desmin **(A)**; S100 **(B)**; CD34 **(C)**; Synaptophysin **(D)**; SALL-4 **(E)**; CD99 **(F)**; CD10 **(G)**; BCL2 **(H)**.

CD34, Synaptophysin, SALL-4, CD99, CD10 and BCL2 are all negative (Figure 9). Given these histomorphologic features and immunoprofile in correlation with the patient's clinical symptoms and physical examination findings, the case was signed out as Wilms Tumor or Nephroblastoma with Favorable Histology.

DISCUSSION

Incidence and clinical presentation

Nephroblastoma or Wilms Tumor represents <1% of all renal malignancies in the adulthood.[2] There has been only one case reported in the Philippines and a few from other countries. Most of the cases are diagnosed following nephrectomy.

Its typical clinical presentation is the same with the pediatric population such as palpable abdominal mass, hypertension, and hematuria.[5] However, findings from other case reports revealed that the main symptom among adults is flank pain associated with weight loss and a sudden drop in performance status.[6,7]

Approximately 10% of nephroblastoma occurs in conjunction with one of several well-defined dysmorphic syndromes.[8] The genetic loci predisposing to nephroblastoma are WT1 and WT2, located in 11p13 and 11p15.5, respectively. Germline point mutations in WT1 are the genetic basis of Denys-Drash syndrome, while deletions of WT1 underlie WAGR syndrome. WT2 is implicated in nephroblastoma associated with Beckwith-Wiedemann syndrome. Inactivation of the WTX gene on the X chromosome occurs in 6%-30% of sporadic nephroblastoma cases. Additionally, activating mutation of the β-catenin gene (*CTNNB1)* is found in 14%-20% of nephroblastoma, leading to disruption of the Wnt signaling pathway.[9]

Diagnosis

The diagnosis of Adult Nephroblastoma is established according to the criteria proposed by Kilton et al (1980). These criteria comprise of the following: (1) The tumor must be identified as the primary renal neoplasm; (2) Presence of primitive blastemal component, spindle or round cell type; (3) Formation of abortive or embryonal tubular or glomeruloid structures; (4) No histologic evidence of renal cell carcinoma within the tumor; (5) Histologic confirmation of the tumor characteristics; and (6) age >15 years old.[10,11] The classic nephroblastoma has three distinct components, making it a triphasic tumor which consists of epithelial, blastemal, and stromal components.[12] These components are present in varying proportions that influence prognosis. Blastemal-predominant nephroblastoma is associated with poor outcomes despite therapy compared to those cases with predominance of epithelial and stromal components.[7]

Prognosis

Prognosis depends on several factors such as age, stage, size, presence of anaplasia, tubular differentiation, post-chemotherapy morphology and TP53 mutation.[9] It has worse prognosis compared in pediatric patients.[13] The prevalence of metastatic disease at the time of diagnosis is significantly higher in adults approximately 30% compared to 10% in pediatric patients. Up to 50% of the cases are already in the advanced stage (Stage III-V). Sites of distant metastasis occur usually in the lungs, liver, and less commonly in the bones, bladder, contralateral kidney, and nervous system.[6,7] Delay in starting chemotherapy within 30 days post-nephrectomy has led to poor event-survival rate of 14.3% (±13%) and overall survivability of 28.6% (±17%) while patients who started treatment within 30 days showed a 5-year event-free survival rate of 60% (±15%) and overall survivability rate of 80%. The National Wilm's Tumor Study Group (NWTS) reported 5-year overall survival rates for adults based on disease stage as follows: stage 1, 100%; stage 2, 92%; stage 3, 70%; and stage 4, 73%. Other published case reports have found poorer outcomes.[14,15]

Additional studies

Immunohistochemistry studies are typically not required for the diagnosis of nephroblastoma but the rare occurrence of this tumor in the adult population raises uncertainty in considering such diagnosis. Several immunostains such as WT1, vimentin, Desmin, CD10, CD99 and other neuroendocrine markers may be helpful in ruling out differential diagnoses of this tumor. In this case, renal cell carcinoma, neuroblastoma, Ewing sarcoma, desmoplastic round cell tumor, and rhabdoid tumor are ruled out by immunohistochemistry studies.

In addition to the routine histopathologic examination, molecular and genetic studies such as cytogenetic analysis may be necessary for clinching the diagnosis.

Treatment

Currently, there is no established treatment guidelines for adult nephroblastoma. Treatment for adult cases is often derived from the already established pediatric protocols. The standard treatment for nephroblastoma involves multimodal approach, with radial nephrectomy and lymph node dissection serving as the foundation of management, typically supplemented by exclusive chemotherapy or concurrent radiotherapy for most patients.[14,15] The limited number of adult nephroblastoma cases results in a lack of clinical studies providing standard management guidelines for this condition.[16,17]

FOLLOW UP AND OUTCOMES

Unfortunately, the patient sought follow-up care after a considerable delay. Treatment has not been initiated yet, as the patient is still undecided.

CONCLUSION

The extreme rarity of nephroblastoma among adults warrants thorough documentation. The limited number of cases worldwide complicates both diagnosis and management. Use of immunohistochemistry studies may be necessary to rule out other differential diagnoses. Prognosis is worse compared in the pediatric population. A standardized model of care and management in adult population needs to be established.

ETHICAL CONSIDERATIONS

Patient consent was obtained for this case report.

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STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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