Role of fine needle aspiration cytology in the management of pediatric renal tumors

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ABSTRACT

Fine needle aspiration cytology (FNAC) is a useful pre-operative procedure in pediatric renal tumors. It is a safe technique that does not upstage the tumor and permits positive diagnosis of Wilm's tumor in almost all aspirates with use of immunocytochemistry for cytokeratin and WT-1. Advanced information on diagnosis of Wilm's tumor, especially, the presence of stroma predominance or anaplastic change is a guide to selection and monitoring of chemotherapy. Early diagnosis of clear cell sarcoma of the kidney (CCSK) by FNAC helps in the evaluation of bone metastasis and selection of Doxorubicin-based chemotherapy protocols to which the tumor is responsive. Thus, the routine use of FNAC is helpful for further investigation and management of pediatric renal masses.

KEY WORDS: Children, fine needle aspiration cytology, renal tumors

Fine needle aspiration cytology (FNAC) has been amply demonstrated to be a useful diagnostic modality in pediatric renal tumors. However, despite this, the exact role of FNAC in evaluation of renal masses of children is unclear and controversial. Primary renal neoplasms on radiology, which are amenable to surgery, require primary resection. This makes the entire specimen available for histopathological evaluation, thereby obviating the need for FNAC prior to operation. On the other hand, inoperable renal tumors require FNAC or biopsy for diagnosis prior to appropriate chemotherapy. FNAC is useful in this situation because in addition to making a positive diagnosis of Wilm's tumor (WT), anaplastic changes of unfavorable WT histology have been seen in aspirates, which may help in selection of the chemotherapy regimen. Other rare pediatric renal tumors like clear cell sarcoma of kidney (CCSK) may be diagnosed prior to starting the chemotherapy. Despite FNAC being a good evaluative technique, increasingly, trucut needle biopsy is being preferred, owing largely to pathologists being unfamiliar with FNAC morphology and the ease of performing immunohistochemistry and molecular biology studies on the biopsy material. It is important to emphasize that neither trucut biopsy nor FNAC upstages pediatric renal tumors. However, the safety of FNAC in this situation is incontrovertible.

Through the 1990s, the All India Institute of Medical Sciences has followed a policy of FNAC being performed in an out-patient setting without anesthesia, in preference to biopsy, in all pediatric tumors. However, in renal tumors, FNAC was performed only in late stage inoperable patients before starting a pre-operative chemotherapy, following the above detailed rationale. FNAC in operable tumors was performed sometimes only when the diagnosis was in doubt on radiological evaluation. Despite this limitation, large numbers of FNACs were performed, and in 2003, a review of a 17-year material found 119 adequate pediatric renal aspirates. This review prompted a rethink, and since 2003, we are performing routine FNAC in all renal tumors of childhood prior to operation.

The vast majority of renal tumors in children are WT. FNAC appearance of WT has been well documented on small series of 15 to 20 cases, including an earlier study from our institution based on an experience of 23 aspirates. Aspirates from WT are cellular and show blastema, tubules, and mesenchymal [Figure 1]. Diagnosis of WT on aspirates that are triphasic or biphasic (with blastema and tubules) is easily accomplished on cytology. However, aspirates showing either only blastema or blastema accompanied by scant mesenchyme, present diagnostic difficulty. Frequently, a
Cytokeratin immunostaining is useful in this regard,
and diagnosis is therefore difficult. One-third of only blastema aspirates from WT have focal cytokeratin positive cells, showing focal epithelial differentiation, which is not otherwise evident on cytology. Recently, WT-1 immunocytochemistry is available, which is always positive in the blastemal cells of WT, except rare instances where both copies of the WT-1 gene are mutated. It is the WT-1 protein which is responsible for blastemal differentiation. We have performed immunocytochemistry for WT-1 on WT aspirates subsequent to 2003 and have found WT-1 to be strongly positive on FNAC smears, with good correlation between histology and cytology. Even poor aspirates with very few tumor cells light up with the WT-1 immunocytochemical stain. Hence, positive diagnosis was possible in aspirates which otherwise would have been reported as scant aspirate with few cells from a malignant round cell tumor. A positive diagnosis of WT is almost always possible on FNAC with use of WT-1 immucytochemistry. Cytomorphology alone is enough for diagnosis of two-thirds of aspirates while immunocytochemistry can resolve the remaining one-third as well. Therefore, FNAC is a useful and less invasive alternative to biopsy.

Stromal predominance was seen in 10% of our WT aspirates [Figure 3], including presence of rhabdomyoblastic differentiation in some instances. Stromal predominance on cytology correlates well with histology and may be an early indicator of chemoresistance. Rhabdomyoblastic differentiation is easy to identify and differentiate from the exceptionally rare pediatric renal rhabdomyosarcoma. Anaplastic (unfavorable) cytological features can be identified on aspirates using criteria similar to histology, i.e., variation in nuclear size of three times or more, marked hyperchromasia with bizarre nuclei, and atypical mitotic figures in a biphasic or triphasic aspirate. If anaplasia is found on FNAC, it is considered as an indication of diffuse anaplasia, which is important since it signifies chemoresistance. When performed, FNAC determines diffuse anaplasia at all instances [Figure 4].

Thus, the main advantage of FNAC in WT is the availability of advanced information before the institution of chemotherapy. Cases with stroma predominance, which do not shrink with chemotherapy and do not behave aggressively, and anaplastic WT, which are chemoresistant, can be separated out. In the latter, a different chemotherapy protocol is indicated. However, so far, the most important advantage of pre-operative FNAC is the diagnosis of CCSK. Of 119 patients, CCSK was diagnosed in 8 patients and rhabdoid tumor in 1 patient.

CCSK, also known as bone metastasis tumor, is not uncommon and forms around 5% of pediatric renal tumors. We found 8 of 119 aspirates (6.72%) to be CCSK; however, this high incidence was mainly among late stage inoperable patients. CCSK has a poor outcome compared to WT and requires a separate chemotherapy regimen incorporating doxorubicin to which it is sensitive. Most cases of CCSK present late and are inoperable in many instances. Pre-operative diagnosis is, therefore, important and possible with FNAC. CCSK differs from WT in its propensity for bone metastasis and needs to be investigated accordingly. Thus, FNAC is a useful guide to further management. The histology of CCSK is only recently described with a large published series. Our experience with FNAC features of CCSK is the largest available to date.

Diagnosis of CCSK on FNAC is a challenge for the cytopathologist because it has many variant patterns. These variations are presently considered as alterations of two kinds of cell types, cord, and septal cells. Septal cells are spindle shaped whereas cord cells are polygonal in shape. It is possible to identify these cells on cytology and this forms the key to diagnosis. The cytopathologist has to be aware of the variable extent of these two cell types, which can be present in aspirates, because sampling of septal cells can lead to a false identification of a “biphasic” pattern and misdiagnosis as WT. Entrapped normal tubules are a feature of CCSK on histology and benign tubular epithelial cells are also commonly seen on FNAC material. These should not be misinterpreted as tubular differentiation of the tumor cells with a misdiagnosis of WT. Cytoplasmic and nuclear features of cord cells are characteristic. The optically clear nuclei of CCSK on histology are seen as fine powdery chromatin on cytology and there are nuclear grooves. Presence of cytoplasm is the most useful criterion. Stromal fragments are composed of septal cells and are embedded in a myxoid matrix which is never seen in WT.

It is important to emphasize that CCSK on FNAC has a variable appearance and knowledge of this variability of cytological features is needed for accurate diagnosis. Unlike WT, there is no positive immunocytochemical marker for CCSK. Vimentin shows focal positivity,
but is much more strongly positive in primitive neuroectodermal tumors and pheochromocytoma, both of which can arise close to the kidney, can resemble CCSK on aspirates, and have a propensity for bone metastasis. CCSK is negative for almost all other immunocytochemical markers, including WT-1. Hence, a complete immunocytochemical panel including vimentin, cytokeratin, WT-1, Mic-2, desmin, and markers for neural differentiation are needed for the diagnosis of CCSK.\(^{[8,23]}\) Negativity for all these other markers is of more importance than positivity for vimentin. In the context of differentiating WT and CCSK, immunocytochemistry for WT-1 is useful, being positive in WT but negative in CCSK. In correlation with radiology, clinical presentation and biochemical findings are also essential.

To conclude, a positive diagnosis of WT on FNAC can be made on morphology and immunocytochemistry in almost all instances. The main advantage of pre-operative FNAC is the early identification of stroma predominance, anaplastic change, and separation from CCSK. Around 10-15% of pediatric renal aspirates have these features. Early availability of this information is useful in further investigations like skeletal survey, bone scan, and PET scan and the chemotherapy protocols to be selected.\(^{[17,24]}\) This is especially so in CCSK, since when compared stage for stage with WT and using

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**Figure 1:** Aspirate from Wilm’s tumor showing blastemal cells and tubules (Papanicolaou, x100)

**Figure 2:** Aspirate from Wilm’s tumor showing blastemal cells with strong nuclear positivity for WT-1 immunocytochemistry, x400

**Figure 3:** Aspirate from Wilms tumor showing predominantly stroma and scant blastema. (Papanicolaou, x100)

**Figure 4:** Aspirate from Wilm’s tumor showing blastemal cells with anaplasia. (Papanicolaou, x400)

**Figure 5:** Aspirate from clear cell sarcoma showing cells with cytoplasm and eccentric placement of nucleus, unlike blastema which has scant cytoplasm. (Papanicolaou, x400)
current management, CCSK has a better outcome than previously thought and approaches the good outcome of WT.[24]

REFERENCES


APPENDIX

The FNAC procedure

A number of advantages make FNAC an attractive investigational modality. The single biggest advantage of FNAC in comparison to biopsy is that it does not require anesthesia, an important benefit in pediatric patients. FNAC is safe, does not harm the patient, gives quick results and importantly, does not upstage a tumor. In a majority of instances, the treating physician gets the answer he is looking for from FNAC, thereby obviating the need for biopsy. However, it is important to be aware of the limitations of FNAC as well. In general, FNAC is usually indicative and not the final diagnostic modality which is histopathology. Cytology is a very subjective science and only an experienced cytopathologist will be able to adequately assist the pediatric surgeon. Cytology cannot be effectively practiced by general histopathologists and the physician must be aware of this limitation.

FNAC is performed using a 22 to 26 gauge needle of adequate length to reach the mass. Most renal masses in children are palpable per abdomen and a one-and-a-half-inch needle is adequate, fitted on a 10 or 20 ml syringe. Using a specially constructed syringe holder permits one handed operation, freeing up the other hand for localizing and stabilizing the swelling. The needle is introduced into the swelling without suction. Then, 5 to 10 ml of suction pressure is applied. Three to five passes of the needle, traversing through the substance of the swelling are made. Then, suction is completely released after which the needle is withdrawn. All material collected within the needle is expelled onto a small area of a slide. A second slide is used as a spreader to spread the material on to one or more slides. Spreading should be even without crushing the material. The smears should ideally be subjected to both alcohol and air dried fixation. The smear should be immersed immediately in 95% alcohol before the material dries in the air and should be sent to the cytopathology laboratory immersed in 95% alcohol. Such smears are suitable for Papanicolaou staining (or Hematoxylin and Eosin in some centers). The air-dried smears are suitable for Giemsa (May Grunwald Giemsa) staining. Papanicolaou stained smears are ideal for evaluating nuclear features and making a diagnosis of malignancy as well as the architectural features for subtyping the tumor. Giemsa stained smears provide additional details regarding cytoplasmic features, which may help in subtyping in some cases.

Complications of FNAC are extremely rare. The only real complication is hemorrhage, which can be problematic in abdominal masses. The incidence of this complication is around 1%, making it very rare. Ideally, overnight observation of the patient should be done. If the patient is going home, the parents should be explained the circumstances for going home, the parents should be explained the circumstances for going home,

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