

Ultrasound-guided co-axial introducer needle biopsy in the diagnosis of eosinophilic cystitis in children

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To the Editor: Eosinophilic cystitis (EC) is a rare condition, characterized by transmural eosinophilic inflammation of the bladder wall, accompanied by increased urine frequency, hematuria, dysuria, and suprapubic pain.^[1] It has rarely been reported in children. The median age at diagnosis in the pediatric population is 6.5 years. There is no standard treatment for EC in childhood, and most patients receive non-steroidal anti-inflammatory agents or steroids as adjuvant therapy.^[2] Most cases in children are self-limiting and do not require more invasive treatments, but serious complications can occur and relapsing forms have been described. Subsequently, there may be a need for long-term monitoring with relevant blood and urine tests and imaging.^[3,4] Biopsy is essential for the diagnosis of EC. Currently, cystoscopy with biopsy is recommended by international guidelines. Cystoscopy biopsy is invasive, cost-intensive. If the disease is confined to the bladder submucosa, without the involvement of the mucosal layer, it is tricky to perform the cystoscopic biopsy, because the whole layer bladder biopsy is not chosen by cystoscopy biopsy. Cystoscopy biopsy is an unpleasant and costly procedure. Thus, it is necessary to develop new diagnostic methods that are less invasive, cheaper, and more accurate for EC diagnosis. We explore the clinical value of ultrasound (US) with bladder wall biopsy in diagnosing EC. Data of 17 patients with bladder masses mimicking neoplasms with a proven diagnosis of EC at Qingdao Women and Children's Hospital between July 2012 and October 2020 were analyzed retrospectively. The inclusion criteria of the patients were the children with bladder variable thickening and bladder irritation symptoms. Children with a history of bladder surgery or topical medication were excluded. This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Qingdao Women and Children's Hospital (No. QFELL-YJ-2021-08) and all participants signed informed consent. Informed consent was obtained from all participants and/or their legal

guardians. The research was conducted under relevant guidelines and regulations.

The patient was laid in the supine position with a fully exposed abdomen. General anesthesia or local anesthesia was then administered. After conventional disinfection, the puncture site was guided by the US to avoid damage to blood vessels, nerves, and vital organs. Under the guidance of the Co-Axial Introducer Needle and the US probe, the outer sheath of the needle was inserted into the outside of the bladder wall. Then, the needle core enters through the sheath into the bladder wall. The direction was adjusted under the guidance of color US dynamic monitoring to make the guidance line pass right through the lesion target. To confirm that the biopsy needle core was inserted into the entire layer of the bladder wall, tissues were taken from different locations. Specimens with a length of >5 mm were required to be selected successfully. We extracted three tissues, all of which were about 10 mm long and 1.4 mm in diameter. The specimens were fixed with 10% formaldehyde solution for the pathological examination [Supplementary Figure 1, <http://links.lww.com/CM9/A602>].

All patients underwent a US-guided needle biopsy of the bladder wall involving all the layers. Computed tomography images of the pelvis showed marked thickening of the bladder wall. Cystoscopy was performed (patients 2 and 16) in another hospital, which revealed areas of mild erythema to gross bullous masses of the bladder wall [Supplementary Figure 2, <http://links.lww.com/CM9/A602>]. The two patients that underwent cystoscopy mucosal biopsy were diagnosed with chronic reactive inflammatory disease [Supplementary Figure 3, <http://links.lww.com/CM9/A602>]. They were commenced on antibiotics for a presumed urinary tract infection, with no resolution of symptoms. They were referred to our institute and eventually underwent a US-guided needle biopsy of the whole layer bladder. Histological examination revealed dense interstitial eosinophilic infiltration in the bladder submucosa and muscularis [Supplementary Figure 4,

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10.1097/CM9.0000000000001564

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Chinese Medical Journal 2021;134(15)

Received: 07-12-2020 Edited by: Li-Shao Guo

<http://links.lww.com/CM9/A602>]. Seventeen of the patients underwent biopsy with the US combined with Co-Axial Introducer Needle. After a US-guided biopsy, one of them had hematuria. Thus, all patients were diagnosed with EC, including six under general anesthesia (≤ 5 years) and 11 through local anesthesia.

From 2012 to 2020, we treated 17 cases of bladder masses mimicking neoplasms with biopsy-proven EC at our institution. There were 13 male patients and four female patients, with ages ranging from 3 to 11 years. Their mean age was 7.3 years. Their major complaints included voiding urgency, frequency, hematuria, and suprapubic pain. We reported from our literature survey that 13 of the 17 pediatric patients suffered from allergic conditions, including egg and environmental allergy, seasonal allergy, medication allergy, and so on. Immunoglobulin E level was abnormal (reference range, 0–200 IU/mL) (patient 5, 6, 7, and 8). In most cases, physical examination was unremarkable. Suprapubic pain was present in five patients (patient 5, 9, 10, 14, and 16). Abnormal findings of laboratory examination included an elevated white blood cell count (reference range, $4.0\text{--}10.0 \times 10^3$ cells/mm³) and the proportion of eosinophils in the peripheral blood were higher (reference range, 0.5%–8.0%). Fourteen cases were found to have significant peripheral eosinophilia [Supplementary Table 1, <http://links.lww.com/CM9/A738>]. Investigations may show proteinuria and microscopic hematuria on urinalysis (patient 3, 4, 5, 7, 8, 13, 14, and 17). Urine analysis showed combined hematuria in four patients and none had proteinuria (patient 2, 5, 8, and 15). Urinalysis revealed protein in the urine (patient 3, 4, 13, and 17). Initial ultrasonography revealed irregular thickening of the bladder wall. Computed tomography images of the pelvis showed marked thickening of the bladder wall.

The etiology of EC is uncertain. The clinical, imaging, and cystoscopy findings are non-specific. Hence, the diagnosis can be missed. We report the findings of our cases in which the diagnosis of EC was confirmed with a US-guided needle biopsy.

Massive eosinophilic infiltrates are noted in the acute phase, but in the chronic phase, eosinophilia is not as prevalent, accompanied by variable chronic inflammation, and prominent scarring. When the lesion is confined to the submucosal layer without invading the mucosal layer, it is not easy to obtain the submucosal tissue under cystoscopy biopsy, and only the pathological report may reveal the chronic inflammatory reaction, which often leads to misdiagnosis. A US-guided biopsy is essential to the establishment of the propria and muscularis, and it will show variable degrees of diagnosis as there is no typical pathological appearance or presenting symptoms. Cystoscopy may have urethral damage and must be performed

under general anesthesia.^[5] A US-guided biopsy under local anesthesia of 11 patients was performed, which is simple and easy to perform, and has high safety. In our study, initial cystoscopy biopsy failed to obtain adequate tissue sampling for two cases. They were commenced on antibiotics for a presumed urinary tract infection with no resolution of symptoms. A US-guided biopsy was performed and made the final diagnosis.

The children with EC may also have bladder tumors. There is a risk of tumor seeding of a track. Although we use Co-Axial Introducer Needle to minimize the possibility of planting transfer, the EC lesion is located on the posterior wall but not on the triangle area or surrounding the ureteral orifices. The number of cases currently is still small, so we will continue to expand the sample size in the next step and explore the mechanism that EC is not located in the triangle area.

To conclude, EC can be a rather tricky condition to diagnose given its lack of unique symptoms and variable presentation. Cystoscopy biopsy is an unpleasant and costly procedure. A US-guided needle biopsy can be performed under local anesthesia in the elderly, avoiding unnecessary cystoscopic trauma and the risk of general anesthesia. A US-guided needle biopsy including all the layers is a feasible method to diagnose this disease, which provides a new way to reduce misdiagnosis. It can be a potential remedy for the failure of cystoscopy diagnosis.

Conflicts of interest

None.

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How to cite this article: Luo YB, Gao Q, Guo J, Zhang Y, Sun J, Li WY, Xiao EL. Ultrasound-guided co-axial introducer needle biopsy in the diagnosis of eosinophilic cystitis in children. *Chin Med J* 2021;134:1872–1873. doi: 10.1097/CM9.0000000000001564