

Percutaneous Perirenal Mass Biopsy in a Sitting Position Revealed Extramedullary Relapse of Acute Lymphoblastic Leukemia

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Abstract. *Background/Aim:* Acute lymphoblastic leukemia (ALL) is a blood malignancy characterized by a rapid proliferation of lymphoid progenitor cells. Extramedullary relapse (EMR) is the recurrence of leukemia that occurs outside the bone marrow. The central nervous system is the most prevalent site of EMR in ALL, whereas other organs, particularly the renal organs, are less commonly involved. *Case Report:* A 49-year-old man diagnosed with Philadelphia chromosome-negative ALL (Ph-negative ALL) received a second umbilical cord blood transplant (uCBT) and was confirmed to be in his third hematological complete remission. However, the perirenal mass lesion emerged after two weeks, and was difficult to detect on echography in the prone position. We successfully performed a percutaneous biopsy of the mass in a sitting position and pathologically identified it as EMR. After the diagnosis, chemotherapy was restarted, and the patient was scheduled to receive a third uCBT. *Conclusion:* This is the first report of EMR in a perirenal lesion of ALL and shows that this novel biopsy can be performed as a renal biopsy, even in a sitting position. This case is the first to describe a biopsy technique in detail and

demonstrates the value of collaboration between hematologists and nephrologists in diagnosing EMR of the kidneys.

Acute lymphoblastic leukemia (ALL) is a malignancy characterized by the transformation and proliferation of lymphoid progenitor cells (lymphoblasts) in the bone marrow, blood, and extramedullary sites. Children account for 80% of all cases of ALL and have a favorable prognosis, whereas adults are less common and have a poor prognosis (1). Although pediatric-based chemotherapy regimens have improved the outcome of adolescent and young adult ALL (2), and hematopoietic stem cell transplantation is performed, the existence of resistant or relapsed disease remains an issue, and new therapies are needed.

Most relapses occur in the bone marrow and peripheral blood. However, cases of extramedullary relapse (EMR) have been reported. EMR in ALL is known to occur mainly in the central nervous system (CNS), while in other sites, particularly in the kidneys, is rare and limited to case reports (3).

Here, we present the case of a 49-year-old man with Philadelphia chromosome-negative ALL (Ph-negative ALL), who developed a third recurrence around the kidney following a second umbilical cord blood transplantation. This case is significant because the recurrence was pathologically identified as EMR with the perirenal kidney biopsy in a sitting position.

This study was performed in accordance with the Declaration of Helsinki and its revisions. The authors declare that informed, voluntary, and written consent for publication was obtained from the patient described in this article.

Case Report

A 49-year-old man with no medical history was diagnosed with Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph-negative ALL) in December 2019. The patient

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Key Words: Acute lymphoblastic leukemia, extramedullary relapse, umbilical cord blood transplantation, kidney biopsy.

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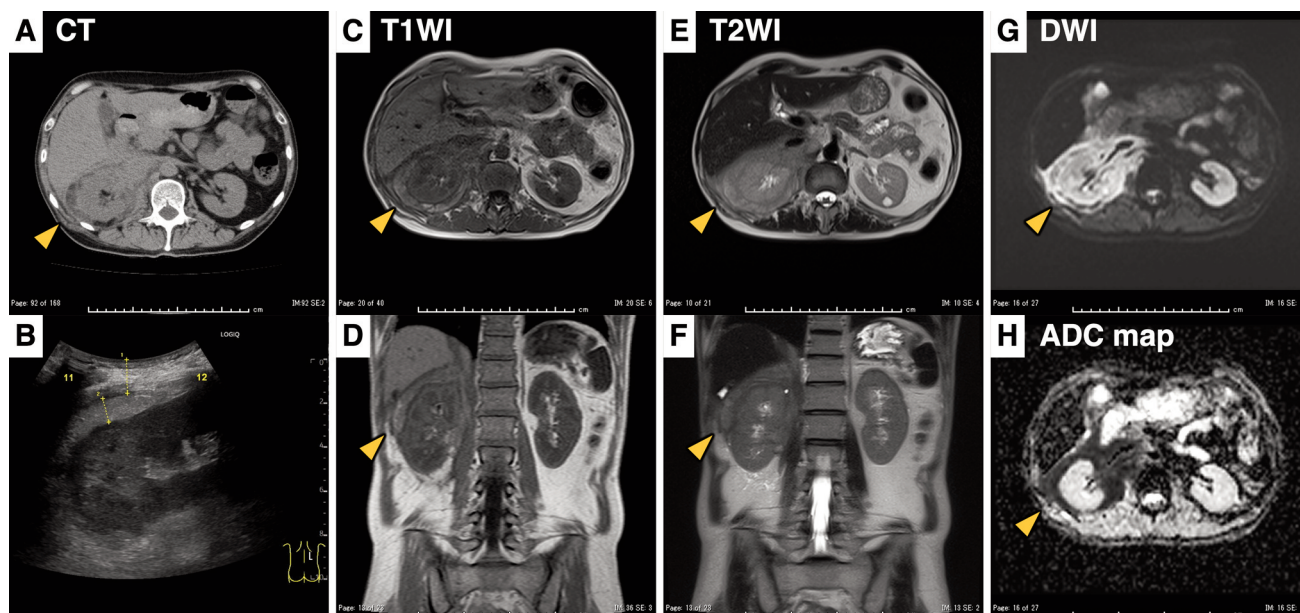


Figure 1. Images of the relapse region on the kidney capsule. (A) Computed tomography shows that the right kidney is enlarged, and a soft tissue mass has formed around it. (B) Echography of the right kidney shows the thickness of the kidney capsule as a high echoic mass lesion from the 11th intercostal space in the sitting position. The distance from the body surface to the lesion was 15.3 mm, and a lesion thickness of 11.0 mm. (C-H) Magnetic resonance images. (C-D) T1 weighted images (T1WI) indicate isointensity. (E-F) T2 weighted images (T2WI) indicate isointensity. (G) Diffusion-weighted images (DWI) exhibit high intensity, and (H) apparent diffusion coefficient (ADC) reveals low intensity, indicative of diffusion depression.

underwent chemotherapy and achieved his first hCR. He received five courses of consolidation therapy and 17 courses of maintenance therapy with methotrexate (MTX) and 6-mercaptopurine 17 times. However, in October 2021, the patient was diagnosed with the first relapse of Ph-negative ALL, with blast cells emerging in his peripheral blood and bone marrow. The patient achieved a second hCR after three courses of blinatumomab and intrathecal injections of MTX and cytarabine. In May 2022, he received his first umbilical cord blood transplantation (uCBT). On day 12, the stem cells were engrafted, and on day 53, bone marrow aspiration (BMA) confirmed complete remission of the ALL. The patient was followed up during an outpatient visit.

On day 264, following the first uCBT, he was diagnosed with a second relapse of ALL, with blast cells emerging in his peripheral blood and bone marrow. He started chemotherapy again, blinatumomab following CHOP-E therapy, and intrathecal injections of MTX, cytarabine, and prednisolone. The third hCR was confirmed using BMA. In May 2023, he underwent a second uCBT. The stem cells were engrafted on day 12, and BMA confirmed complete remission of ALL on day 51.

On day 66 following the second uCBT, the patient developed right lateral abdominal pain. Computed tomography revealed a mass involving retroperitoneal adipose tissue around the kidney (Figure 1). On magnetic resonance imaging,

the mass had iso-intensity on T1 and T2 weighted images, high intensity on diffusion-weighted images (DWI), and low intensity on apparent diffusion coefficient (ADC). These findings suggested that this lesion was a perinephric abscess or lymphoblastic cell invasion. Echography revealed that the mass was highly echoic between the liver and kidney with a thickness of approximately 1 cm. It was difficult to detect in the prone position, but it moved caudally and could be observed in the sitting position. The primary hematologist asked us to perform a biopsy to determine the lesion.

Percutaneous kidney capsule biopsy in a sitting position.

On day 73, we performed a sitting percutaneous perirenal mass biopsy in the same manner as a kidney biopsy. Figure 2 shows procedure images of the biopsy. The patient sat on the edge of the bed, leaning against the overbed table. We reconfirmed the location of the mass and marked the puncture site on the skin (Figure 2A). Puncturing from the 11th intercostal space seemed safe in the present case. We administered local anesthetic just above the lesion. We tried a fine needle aspiration first, but nothing was aspirated, assuming the lesion was not an abscess. We then switched to performing a biopsy. We inserted the same needle biopsy gun used for the kidney biopsy and collected specimens by checking the tip of it by echography (Figure 2B and C). Following the biopsy, we compressed the

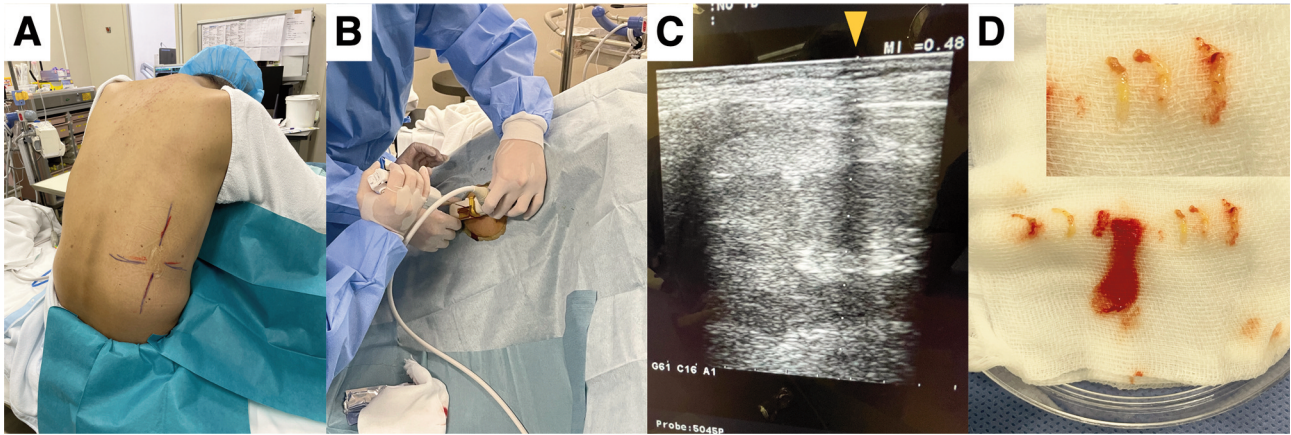


Figure 2. Procedure images of the percutaneous perirenal mass biopsy. (A) The patient sat on the edge of the bed, bending forward to lean against the overbed table. (B) Ultrasound was used to identify the thickened capsule between the skin and kidney cortex. A specimen was collected with a needle biopsy gun typically used in percutaneous kidney biopsies. (C) A photograph of the echography screen during the biopsy. The biopsy needle was inserted through the arrowhead in the figure, and an acoustic shadow caused by the needle is visible at the biopsy site. (D) Specimen of the thickened kidney capsule immediately after the biopsy.

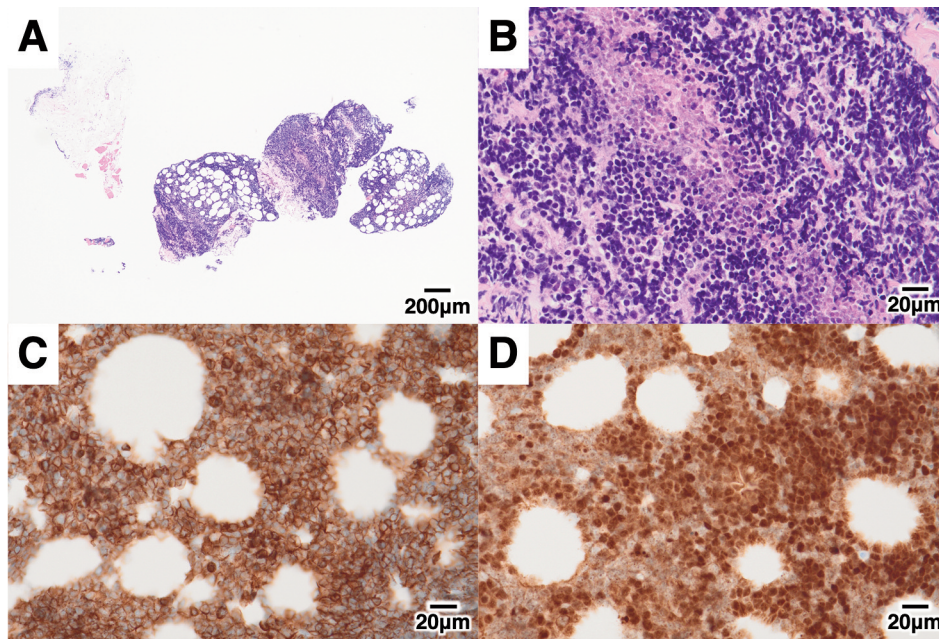


Figure 3. Pathology of the perirenal mass showing lymphoblastic cell infiltration. (A) A proliferative lymphoblastic infiltration with a high N/C ratio dividing or diffusely infiltrating between adipocytes in the retroperitoneum. The lymphoblasts exhibit fine chromatin and mildly malformed nuclei. (40× magnification). (B) Hematoxylin and eosin staining of the lymphoblasts (400× magnification). (C) Immunohistochemistry of CD79. Cells express it in the cytoplasm (400× magnification). (D) Immunohistochemistry of TdT. Cells express TdT in the nucleus (400× magnification).

puncture site manually for about 10 minutes before confirming with echography that there was no bleeding or other complications related to the puncture, and finished the biopsy. Six cores were collected for pathology and flow cytometry (Figure 2D).

Flow cytometry analysis revealed the following cell populations: CD10+, CD19+, CD20–, CD22+, CD34+, and CD38+, without light chain expression, indicating the existence of B lymphoblastic cells. Figure 3 shows the pathology of the specimens. It demonstrated a proliferative

lymphoblastic infiltration with a high nucleus-cytoplasm (N/C) ratio diffusely invading among adipocytes (Figure 3A and B). Immunohistochemistry revealed B lymphoblastic cells positive for terminal deoxynucleotidyl transferase (TdT) and CD79, but negative for CD3 and myeloperoxidase. These results identified the thickened kidney capsule as a relapse of Ph-negative ALL.

After the diagnosis, blasts emerged again in his peripheral blood at 9.5% on day 76 and increased to 40.5% on day 78. He restarted blinatumomab on the same day but switched to inotuzumab ozogamicin on day 90 because of cytokine releasing syndrome and pancreatitis. The patient is scheduled to receive a third uCBT.

Discussion

This case highlights two significant points. First, the biopsy revealed EMR of ALL in the perirenal mass lesion. While the most common EMR of ALL involves the central nerve systems (CNS), isolated EMR sites, such as the kidneys, are uncommon. Fielding *et al.* reported in 2007 that 45 of 609 (8%) adult ALL relapsed at isolated extramedullary sites, with only one EMR on the kidney (4). Ge *et al.* reported in 2014 that the cumulative incidence of EMR following allogeneic HSCT was 12.9%. However, EMR to the kidney was not demonstrated (3). Some case reports indicate renal EMR in adults with ALL. Skeith experienced a relapse with only chemotherapy (5). Sato described the one following bone marrow transplantation (6). Jimenez-Ochoa reported the one after allogeneic peripheral blood stem cells (7). These reports showed that their EMRs emerged on both kidneys, lymphoblastic cells invaded and surrounded the glomeruli and tubules, and they developed acute kidney injury. However, our case is unique. The EMR was limited to the unilateral kidney capsule, causing pain without invading the kidney or affecting renal function - to our knowledge, the first such case.

The second point is the procedure performed in a sitting position instead of a prone one. Ivasen and Brun pioneered the percutaneous aspiration kidney biopsy in 1951 (8), and Kinoshita of Niigata University established the procedure of kidney biopsy in Japan in 1954 (9). Although it is now conventional to perform a kidney biopsy in the prone position, the sitting position was the first being used. Therefore, as in this case, the sitting biopsy was an application of our forefathers' concept. Amini *et al.* found no difference in the number of obtained glomeruli and procedure-related complications between sitting and prone kidney biopsies, and a sitting position is more comfortable than a prone position (10). In this case, the malignancy was difficult to observe in the prone position, making the sitting position more suitable, especially as the kidney needed to migrate caudally for reliable specimen collection.

Radiographic imaging is crucial for detecting EMRs. However, as Sava *et al.*, who found atypical EMRs using 2-Deoxy-2-(fluorine-18)fluoro-D-glucose (18F-FDG-PET/CT), reported, histological investigation is the only way to achieve a conclusive diagnosis (11). In this case, distinguishing between an abscess and an EMR was challenging, emphasizing that radiographic investigations initiate suspicion of EMR, but a definite diagnosis requires obtaining tissue samples and identifying leukemic cell infiltration. Whereas many reports focus on detecting EMRs using radiological approaches, none discuss biopsy methods. Our case is the first to describe a biopsy technique in detail.

Conclusion

We successfully diagnosed the relapse of Ph-negative ALL by performing a percutaneous perirenal mass biopsy in a sitting position. This case highlights that even if hematologists are inexperienced with performing a biopsy of challenging lesions surrounding the kidney, a nephrologist skilled in kidney biopsy may be able to perform the procedure. This case underscores the value of collaboration between hematologists and nephrologists in diagnosing EMR around the kidney.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

Yuki Oba: Methodology, Investigation, Data Curation, Writing-Original draft, Visualization. Ryo Koizumi, Kosei Kageyama, Masatoshi Yoshimoto: Resources, Investigation. Shigekazu Kurihara, Daisuke Ikuma, Kyosuke Yamaguchi, Masayuki Yamanouchi, Tatsuya Suwabe, Kazuya Ishiwata: Resources. Atsushi Wake: Resources, Writing-Review & Editing. Yoshifumi Ubara: Writing-Review & Editing. Naoki Sawa: Conceptualization, Methodology, Writing-Review & Editing, Supervision.

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References

- 1 Terwilliger T, Abdul-Hay M: Acute lymphoblastic leukemia: a comprehensive review and 2017 update. *Blood Cancer J* 7(6): e577, 2017. DOI: 10.1038/bcj.2017.53
- 2 Hayakawa F, Sakura T, Yujiri T, Kondo E, Fujimaki K, Sasaki O, Miyatake J, Handa H, Ueda Y, Aoyama Y, Takada S, Tanaka Y, Usui N, Miyawaki S, Suenobu S, Horibe K, Kiyoi H, Ohnishi K, Miyazaki Y, Ohtake S, Kobayashi Y, Matsuo K, Naoe T, Japan Adult Leukemia Study Group (JALSG): Markedly

- improved outcomes and acceptable toxicity in adolescents and young adults with acute lymphoblastic leukemia following treatment with a pediatric protocol: a phase II study by the Japan Adult Leukemia Study Group. *Blood Cancer J* 4(10): e252, 2014. DOI: 10.1038/bcj.2014.72
- 3 Ge L, Ye F, Mao X, Chen J, Sun A, Zhu X, Qiu H, Jin Z, Miao M, Fu C, Ma X, Chen F, Xue S, Ruan C, Wu D, Tang X: Extramedullary relapse of acute leukemia after allogeneic hematopoietic stem cell transplantation: Different characteristics between acute myelogenous leukemia and acute lymphoblastic leukemia. *Biol Blood Marrow Transplant* 20(7): 1040-1047, 2014. DOI: 10.1016/j.bbmt.2014.03.030
 - 4 Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, Durrant IJ, Luger SM, Marks DI, Franklin IM, McMillan AK, Tallman MS, Rowe JM, Goldstone AH, Medical Research Council of the United Kingdom Adult ALL Working Party, Eastern Cooperative Oncology Group: Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood* 109(3): 944-950, 2007. DOI: 10.1182/blood-2006-05-018192
 - 5 Skeith L, Lazo-Langner A, Mangel J: Kidney and pancreatic extramedullary relapse in adult acute lymphoblastic leukemia: a case report and review of the literature. *Case Rep Hematol* 2013: 637264, 2013. DOI: 10.1155/2013/637264
 - 6 Sato A, Imaizumi M, Chikaoka S, Niizuma H, Hoshi Y, Takeyama J, Fujii K, Nishio T, Watanabe M, Maesawa C, Hayashi Y, Iinuma K: Acute renal failure due to leukemic cell infiltration followed by relapse at multiple extramedullary sites in a child with acute lymphoblastic leukemia. *Leuk Lymphoma* 45(4): 825-828, 2004. DOI: 10.1080/10428190310001593148
 - 7 Jimenez-Ochoa MA, Contreras-Serratos MM, Gonzalez-Bautista ML, Lopez-Macias C, Lozano-Jaramillo DA: Isolated renal relapse in a post-allogeneic transplant adult patient with acute lymphoblastic leukemia. *J Med Cases* 13(10): 499-503, 2022. DOI: 10.14740/jmc4003
 - 8 Iversen P, Brun C: Aspiration biopsy of the kidney. *Am J Med* 11(3): 324-330, 1951. DOI: 10.1016/0002-9343(51)90169-6
 - 9 Ubara Y, Kawaguchi T, Nagasawa T, Miura K, Katsuno T, Morikawa T, Ishikawa E, Ogura M, Matsumura H, Kurayama R, Matsumoto S, Marui Y, Hara S, Maruyama S, Narita I, Okada H, Tsuruya K, Committee of Practical Guide for Kidney Biopsy 2020: Kidney biopsy guidebook 2020 in Japan. *Clin Exp Nephrol* 25(4): 325-364, 2021. DOI: 10.1007/s10157-020-01986-6
 - 10 Amini M, Ganji MR, Najafi I, Hakemi MS, Soleymanian T, Yaghoubi F, Tavakoli F, Sheikh V, Yousefi A, Afrasiab AA, Movassaghi A, Amini H: Percutaneous biopsy of kidney; comparison between prone position and sitting position. *Iran J Kidney Dis* 13(5): 300-303, 2019.
 - 11 Sava CN, Ritli L, Balmoş AB, Iuhas AR, Marian P, Motorca MA, Lele LA, Straciuc O, Zaha DC, Jurcă MC, Niulaş L, Negruţ N: Unusual extramedullary relapses in a case of common B-cell acute lymphoblastic leukemia. Case report and review of literature. *Rom J Morphol Embryol* 60(1): 249-254, 2019.

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