

CASE REPORT

Unusual extramedullary relapses in a case of common B-cell acute lymphoblastic leukemia. Case report and review of literature

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Abstract

Background: Acute lymphoblastic leukemia (ALL) represents the most common malignancy in children with an overall cure rate of 85%. Relapses occur in 20% of the cases. Commonly, extramedullary relapses (EMRs) involve central nervous system (CNS) or testes. Unusual EMRs in ALL are relatively rare reported. **Case presentation:** The authors present a 24-year-old woman with ALL, who experienced three unusual EMRs. In 2007, she was diagnosed with B-cell precursor (BCP)-ALL – high-risk (HR) group, and she was treated according to ALL Intercontinental Berlin–Frankfurt–Münster (IC-BFM) 2002/HR Protocol. She entered complete remission (CR). In 2012, a vaginal wall solid mass infiltrate occurs. Biopsy concluded for EMR of ALL. Chemotherapy was restarted; the patient responded again with CR. Magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) examinations during follow-up revealed supraclavicular, mesenteric, and retroperitoneal lymphadenopathies (2014). Pathological examination of the supraclavicular lymph node showed a benign pattern: schwannoma. The patient's evolution worsened, imposing a biopsy from the retroperitoneal tumor which revealed a second EMR of ALL. Again, ALL-REZ BFM 2002 Protocol was started, followed by haploidentical mother-to-child peripheral blood hematopoietic stem cell transplantation (HSCT). After suffering a few managed complications related to the transplant, our patient achieved CR again. In 2017, 10 years after the initial diagnosis, the patient presented for the third time an EMR (gastric wall) and eventually died due to progression of the disease. **Conclusions:** The patient presented an extremely aggressive type of ALL with three unusual EMRs: vaginal, retroperitoneal and gastric.

Keywords: leukemia, teenage girl, unusual extramedullary (vaginal, retroperitoneal, gastric) relapses.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. It represents about 25% of all childhood cancers. Overall cure rates for childhood ALL improved constantly from the middle of the last century due to advances in developing active chemotherapeutic drugs, modern protocols and significant improvement of supportive care therapy. Nowadays, event-free survival (EFS) rates for this disease range between 75% and 85%, and there are some ALL subgroups of patients having an overall cure rate greater than 90% [1].

Despite of these progresses, relapse of ALL still occurs in 15–20% of cases. Most relapsed ALL will maintain the initial immunophenotype. Bone marrow (BM) relapse remains the main manifestation of treatment failure of patients with ALL, but around 5% of ALL relapses occur in extramedullary (EM) sites alone. Usually, extramedullary relapse (EMR) in patients with ALL involves the brain or testis. EMR involving female genitourinary system it is more likely in lymphoma, rather than leukemia. Relapse of ALL in gynecological organs is extremely rare, involving usually the testis, female genital system being

much more rarely affected [2]. Female genital tract affecting is rare in hemato-oncological diseases, including cases of ovarian involvement in ALL, with just a few cases being reported in the literature. Pelvic masses as sites for EMR of ALL are only exceptionally reported in females [3].

EMR after hematopoietic stem cell transplantation (HSCT) is relatively rare. The incidence of EMR after HSCT has been reported to range from 6–20%. In general, the incidence of EMR after HSCT is higher in patients with ALL than in those with acute myeloid leukemia. A recent report showed that the estimated 10-year cumulative incidence of EMR after HSCT was 12.9% in patients with ALL. The most commonly reported sites in ALL patients after HSCT are soft tissue and the central nervous system (CNS) and the gastrointestinal (GI) system is an uncommon site. There have been only a few case reports of GI relapse after HSCT [4].

The authors present the case of a teenage girl, who was diagnosed and treated for ALL at the Department of Pediatric Oncology and Hematology, "Dr. Gavril Curteanu" Municipal Clinical Hospital, Oradea, Romania, since 2007. She was included in the high-risk (HR) group of

patients with ALL according to the risk stratification criteria for childhood ALL. The patient described here had an extremely aggressive evolution of leukemia, and, after achieving complete remission (CR), she presented three unusual, extremely rare EMRs: first she developed a vaginal mass (lymphoblastic infiltrate), then a retro-peritoneal leukemic relapse, and, finally, lymphoblastic infiltrates of gastric wall. The patient died in 2018 due to the progression of the disease.

The aim of this case report is to increase awareness to this uncommon relapse sites, as this presentations may become a more frequent situation considering that the number of ALL long-term survivors is increasing. The radiological features help to recognize these lesions but, due to the unusual sites, definitive diagnosis can be made only by histological analysis, and immunophenotyping.

This study was approved by the Ethics Committee of our Hospital, and written informed consent for data access was obtained from the patient's family.

Case presentation

We report the case of L.D., a 24-year-old female from Bihor County (Romania), diagnosed with B-cell precursor (BCP)–ALL. The patient experienced a highly aggressive form of leukemia, presenting three successive EMRs, while in BM remission.

In October 2007, at the age of 14, she was referred to the Department of Pediatric Oncology and Hematology, “Dr. Gavril Curteanu” Municipal Clinical Hospital, Oradea (Clinical Observation Form No. 8847/2007) presenting prolonged fever, malaise, pallor and generalized lymph node enlargement. Complete blood count revealed the presence of B-lineage lymphoblasts (17%) in the peripheral blood and BM aspiration confirmed the presence of blasts in a proportion of 96% (Figure 1, a and b). Immunophenotyping analysis revealed positive expression for cluster of differentiation (CD) 10, CD19, CD20, CD22, CD34, cyCD79a, CD58, CD38, CD9 (Table 1).

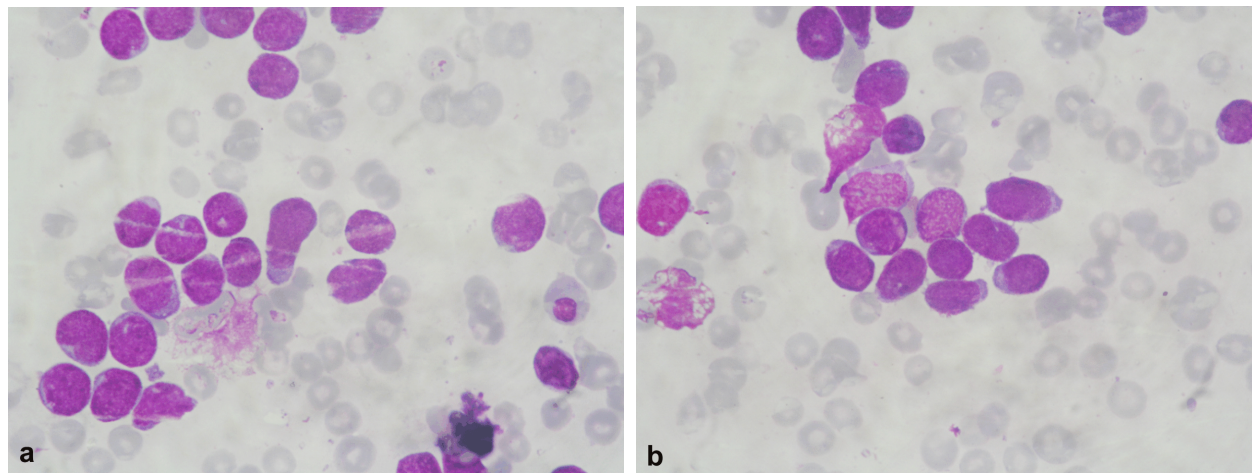


Figure 1 – (a and b) Immature lymphoid population, with a mainly insular disposition and a cytomorphological aspect of lymphoblasts; most of the lymphoblasts are of average size, nuclear irregularity, cleaved nucleus, homogenous distribution of chromatin, presence of nucleoli and reduced, basophilic cytoplasm. Peripheral blood sample; Hematoxylin–Eosin (HE) staining: (a and b) $\times 100$ (October 2007).

Table 1 – B-cell ALL immunophenotype

Lymphoid antigen expression	Not-expressed antigens
CD10+; CD19+; CD20+; CD22+; CD34+; cyCD79a+; CD58+; CD38+; CD9dim+; CD45-; CD24-	cyCD3; cyMPO; CD7; smCD3; smIgKappa; cyIgM; CD33; smIgM; CD117; CD13; smIgLambda

ALL: Acute lymphoblastic leukemia; CD: Cluster of differentiation; cy: Cytoplasmic; MPO: Myeloperoxidase; sm: Surface membrane; Ig: Immunoglobulin.

Cytogenetics was negative. She was diagnosed with BCP–ALL, HR group (12% blasts on day 33 of treatment). She started chemotherapy according to ALL Intercontinental Berlin–Frankfurt–Münster (IC–BFM) 2002 Protocol combined with prophylactic cranial radiotherapy (pCRT), total dose 12 Gray (induction therapy with Vincristine, Prednisone, Cyclophosphamide, Doxorubicin, and L-Asparaginase, followed by HR' blocks and maintenance therapy with 6-Mercaptopurine, Methotrexate, Prednisone and Vincristine; intrathecal Methotrexate was administered throughout). She achieved CR and finished the maintenance therapy in August 2010.

During follow-up evaluation, in January 2012, 17 months after the end of treatment, she presented with an

oval infiltrative mass, relatively well-defined, measuring 4/2.8/3 cm, with a parenchymal, non-homogeneous structure, showing positive Doppler signal, located most likely in the vaginal wall, detected during abdominal ultrasound examination. The magnetic resonance imaging (MRI) series confirm the presence of a 35/55/45 mm solid tumor located at the anterior wall of the vagina, no signs of invasion of the adjacent organs, but possible extension to neighboring ganglia (bilateral iliac lymphadenopathy) (Figure 2). Cytomorphological and flow cytometric immunophenotypic findings (CD10+, CD49+) of the tumor biopsy confirmed EMR of ALL (Figure 3).

In January 2012, chemotherapy according to ALL–REZ BFM 2002 Protocol for relapsed ALL was started (S1 risk group: late isolated EMR, non-T immunophenotype) resulting in CR again. After the completion of induction phase, MRI reassessment performed in September 2012 did not reveal the presence of the vaginal tumor; positron emission tomography/computed tomography (PET/CT) examination was considered appropriate (November 2012) and proved CR (Figure 4, a and b). Maintenance therapy was started in August 2012 and ended in May 2014.

In September 2014, five months after the ALL relapse treatment ended, abdominal ultrasound routine examination showed a retroperitoneal hyperechogenic parenchymal mass of 8.4/2.6 cm, with multiple lymphadenopathies inside (Figure 5). Abdominal CT confirmed the presence of the retroperitoneal mass hinting for possible leukemic infiltrates. Investigations were completed with PET/CT evaluation showing mesenteric, pelvic, and retroperitoneal and supraclavicular metabolically active lymphadenopathy (Figure 6, a–c). BM aspirate was negative for leukemia or other foreign cells infiltrates. Histopathological examination of biopsied left supraclavicular lymph node concluded for a benign pattern: schwannoma. The patient's evolution worsened, presenting abdominal pain, subocclusive syndrome and pancreatitis, which imposed a biopsy from the retroperitoneal tumor, revealing a massive tumor infiltrate composed of small cells of lymphoid appearance with hyperchromatic nuclei having the following immunohistochemistry (IHC) profile: leukocyte common antigen (LCA) weak positive, terminal deoxynucleotidyl transferase (TdT) intensely positive, immunocytochemical staining for Ki67 indicating a very high proliferation index (95%), proving a second EMR of ALL (February 2015). ALL–REZ BFM 2002 Protocol was started again in March 2015, with CR in April 2015, followed by mother-to-child HSCT in July 2015 (Italy).



Figure 2 – Vaginal tumor. MRI scan: solid tumor of 35/55/45 mm, situated in the superior 2/3 of the anterior vaginal wall, without any signs of invasion of the neighboring structures (January 2012). MRI: Magnetic resonance imaging.

After HSCT, patient developed a few complications related to transplant: acute cutaneous graft-versus-host disease (GVHD), cytomegalovirus (CMV) reactivation, chronic hepatic GVHD, sepsis, all managed by multi-disciplinary medical team.

In 2017, 10 years after the initial diagnosis, the patient, now adult, presented the third EMR of ALL involving the gastric wall and eventually died due to progression of the disease.

Discussions

The aim of initial ALL treatment is induction of remission. Patients in CR have no evidence of leukemia (normal physical findings, peripheral blood within normal ranges, fewer than 5% blasts in BM, absence of detectable CNS or EM disease). Nowadays, the 5-year overall survival rate of pediatric ALL in developed countries reaches 85–90% [5, 6].

Still, relapse occurs in about 10–15% of these patients with ALL, and patients who relapse are more difficult to treat. In this stage, the results are comparably worse, with long-term survival rates up to only 30–35% [7]. Due to the high prevalence among pediatric cancers, relapsed ALL represents the main cause of cancer-related deaths in children, 10% to 15% of patients with ALL still dying of their disease.

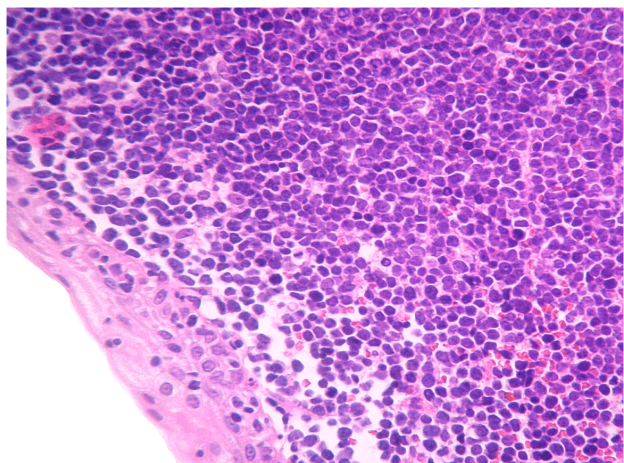


Figure 3 – Massive infiltration of lymphoblasts of B-cell lineage (CD10+ CD49+). Vaginal wall mass biopsy; HE staining, ×100 (February 2012). CD: Cluster of differentiation; HE: Hematoxylin–Eosin.

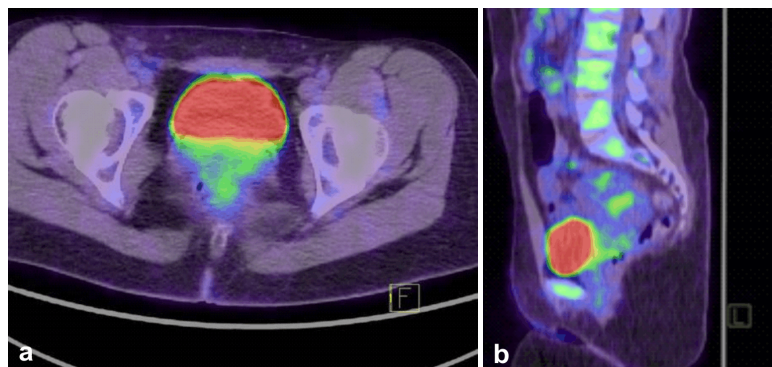


Figure 4 – Axial and sagittal PET/CT fusion images. No vaginal morpho-metabolic alterations – complete remission (November 2012). PET/CT: Positron emission tomography/Computed tomography.

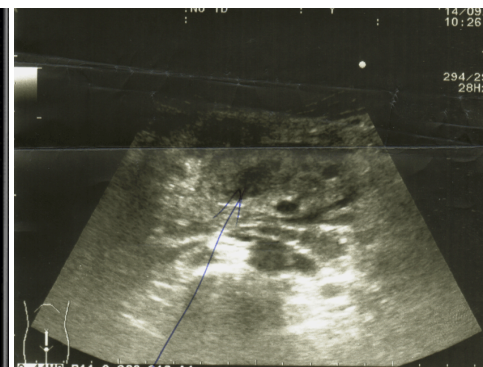


Figure 5 – Retroperitoneal mass on ultrasound examination (September 2014).

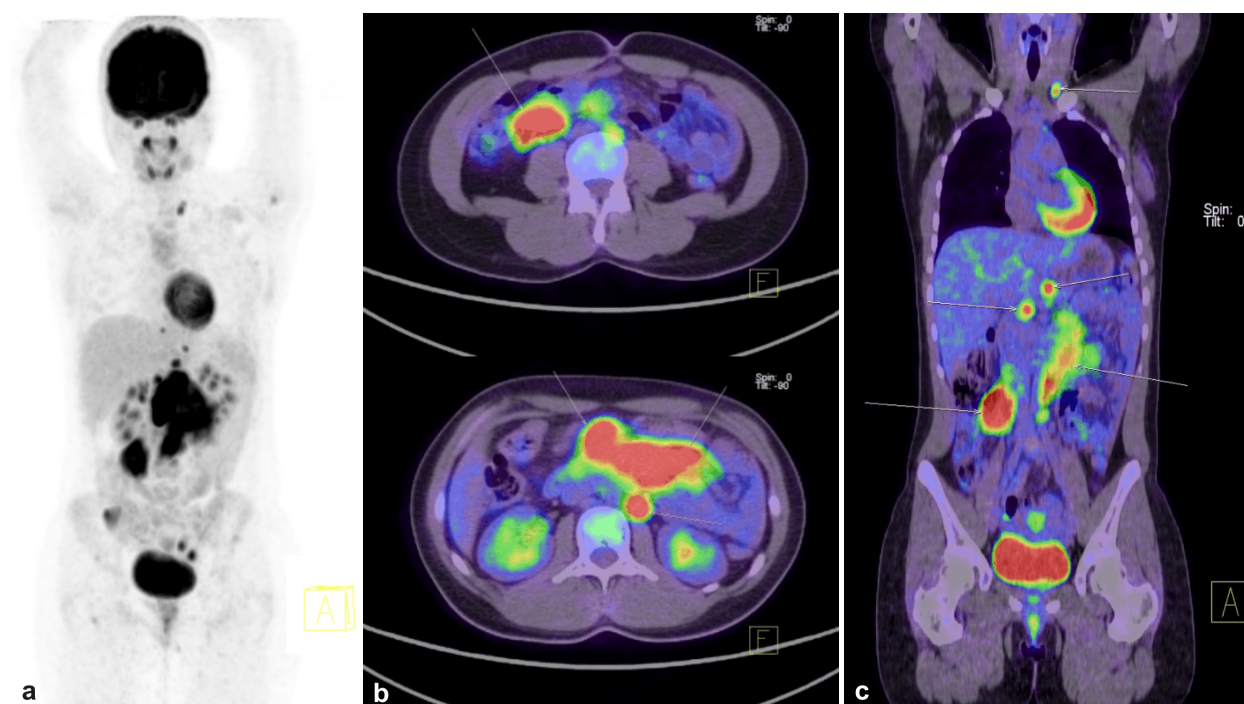


Figure 6 – PET image and PET/CT fusion images; axial and coronal plane. Retroperitoneal tumor. ALL relapse. Left supraclavicular adenopathy, mesenteric and retroperitoneal metabolically active lymphadenopathy (October 2014). PET: Positron emission tomography; CT: Computed tomography; ALL: Acute lymphoblastic leukemia.

It had been demonstrated that non-meningeal EM leukemic foci are commonly present in patients during apparent continuous CR. Furthermore, many reports have documented that the incidence of EM leukemia increases with prolonged survival. Certain prognostic factors have been established to evaluate ALL after relapse, and the identification of such items is essential in common practice to assign patients into different risk groups and treatment management is tailored accordingly; among this factors, the time interval and the site of the relapse together with the immunophenotype, are the most generally considered parameters. A better prognosis was found in relapse at isolated EM sites, such as CNS or testis, while isolated BM relapse has a poorer prognosis, and mixed EM and BM relapse falls between the two [8].

Since widespread leukemic infiltrates have been found at necropsy and in studies on children in apparent remission, other EM sites, apart from the meninges and testes, could well present further problems for therapy [9]. Uncommon sites affected in ALL are represented by the female genital organs, like the ovaries and cervix. Sahu *et al.* in a 2015 article stated that ovarian masses are usually taken as a germ cell malignancy in younger girls, even if they were previously diagnosed with ALL. A higher level of suspicion needs to be kept while assessing these symptoms in ALL patients. EMR occurs more commonly in AML, with lymph nodes and skin being the more frequent sites involved [10]. Also, rarely observed in ALL is the EM tissue infiltration as a solid tumor, feature that is common of the AML. The medical literature reports the pleura, mediastinum, pancreas or spinal cord being rare sites of ALL relapse [11].

Despite the success of CNS preventive therapy in case of ALL, CNS remains the most common site of EMR. Several studies mentioned the infiltration of gonads by

leukemic blasts, demonstrated during autopsy in ALL cases [9, 12]. Testicular relapse is far more frequent site of EMR when compared with ovaries, Sasidharan *et al.* reported [3]. With only seldom cases reported, implication of the female genital tract in hematological cancers is rare; and the involvement of the ovary or cervix as an isolated clinical primary site of relapse is uncommon [13, 14]. Due to abdominal symptoms being indistinct and uncharacteristic, patients usually present to a surgical or a gynecological office and often the diagnosis is obtained after pathological examination of biopsied/resected specimens [10]. In two studies, conducted by Pais *et al.* (23 cases) and Kim *et al.* (31 cases), ovarian involvement in ALL is reviewed [15, 16]. In these surveys, it was showed that the average time interval from initial ALL diagnosis to the ovarian EMR was 53.7 months and no correlation was established between the type of cytostatic drug combination used and the risk of progressing to ovarian relapse [15]. In another study, from 1995, Qamruddin *et al.*, reviewing several autopsy reports series, found an incidence of ovarian leukemic infiltrates between 11% and 50% compared with 29% to 92% incidence of testicular leukemic involvement in patients with BM relapse. These findings were described post-mortem, and similar data were rarely reported during the clinical evolution of ALL. The ovaries and the testis represent sites in which the leukemic cell have been present from the initial malignant transformation and stayed asymptomatic during the course of the ALL [17].

Even more rarely reported during the follow-ups of female patients treated for ALL is the pelvic relapse. Metastatic lymphoblasts invading these regions may find favorable conditions for survival and may subsequently lead to a recurrence of the disease. Experimental models investigating the spread of malignant cells in the

peritoneum following intraperitoneal inoculation and demonstrating the infiltration of areas rich in “milky spots”: gonadal fat, the mesentery or the omentum have been reported by Hagiwara *et al.* and, more recently, by Kantekure *et al.* [18–20]. Only a few cases of pelvic ALL relapse are reported in the literature, most of these being diagnosed during autopsies. Patients being diagnosed ante-mortem with this unusual type of solid mass lymphoblastic infiltrate are even rarer, but as a patient to present two successive pelvic relapses are really exceptional.

Considering that patients treated with the new chemotherapy regimens have a longer survival rate, the pelvic EMR of leukemia, now unusual, may become more common in female patients with ALL. For this reason, a closer monitoring of the pelvic region in girls diagnosed with ALL may be required during follow-up [17]. Our patient survived for almost a decade after being diagnosed with ALL, considering that she was included in the HR group from the beginning. First pelvic EMR was diagnosed during a routine follow-up ultrasound examination of the abdomen. With the exception of ovaries, other pelvic relapses are difficult to diagnose in the early stages. A useful method to identify them could be pelvic ultrasound, but its use as a screening method in monitoring ALL requires further evaluation [3, 21].

Involvement of the GI tract occurs in approximately one quarter of patients with ALL, especially on account of relapses, usually being an autopsy finding. Leukemic infiltrates are most prevalent in the stomach, ileum and proximal colon. According to Ebert & Hagspiel, the main causes of death in GI leukemia are hemorrhage, infections and necrotizing enterocolitis [22, 23].

The most commonly reported sites in ALL patients after HSCT are soft tissue and the CNS and the GI system is an uncommon site. There have been only a few case reports of GI relapse after HSCT [4].

With the exception of CNS involvement, other isolated EMR sites of ALL are rare and generally involve soft tissues, which may be difficult to detect and properly diagnose using radiological imaging methods, because the CT cannot distinguish between lesions caused by chemotherapy and radiotherapy and tumor relapse. 2-Deoxy-2-(fluorine-18)fluoro-D-glucose (^{18}F -FDG-PET/CT) is a particularly sensitive method in finding the site and the metabolic activity of a relapsed cancer lesion. This investigation is not generally used for the stadialization of acute leukemia but can be of real help in identifying BM relapse or unusual EMR. Its application in cases of ALL remains limited [24–26]. However, radiological features do help in recognizing these lesions; definitive diagnosis can be made only by histological analysis and immunophenotyping [27].

✉ Conclusions

Typically, patients with relapsed ALL refer to pediatric onco-hematologist due to events related to BM invasion. Nevertheless, sometimes the leukemia relapse is involving only EM sites, including genital tract or pelvis, much more rarely GI tract. Therefore, it requires the involvement and awareness of specialists in other areas, such as gynecologists, gastroenterologists, radiologists, regarding

the possibility that leukemia may embrace the appearance of solid tumor infiltrates. Our patient presented three unusual EMRs, vaginal, retroperitoneal, and gastric, considering involvement of female genital tract or GI tract by ALL being infrequent. She survived for 10 years to a very aggressive type of ALL. The case is presented due to its rarity.

Conflict of interests

The authors declare that they have no conflict of interests.

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