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CASE REPORT

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Uterine recurrence of acute lymphoblastic leukemia: diagnosis, treatment and literature review

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Abstract

Background: Extramedullary relapse of B-cell acute lymphoblastic leukaemia (B-ALL) occurs in 2–6% of cases, with the central nervous system and testes being the most commonly affected sites. Infiltration of gynaecological organs is an exceedingly rare occurrence, with the majority of documented cases pertaining to the ovary. **Case**: This study presents the case of a 14-year-old girl with extramedullary relapse of B-ALL in the uterus, following intensive chemotherapy and immunotherapy with inotuzumab. The patient presented with symptoms of abnormal uterine bleeding and severe pelvic pain. She was treated with surgical intervention (bilateral hysterosalpingo-oophorectomy) and subsequently received chimeric antigen receptor T-Cell (CAR-T19) therapy, yet the disease remained refractory. It is possible that CAR T-cell therapy may be more effective at penetrating extramedullary sites, although relapses can occur, in a manner similar to that observed with haematopoietic stem cell transplantation. **Conclusions**: Uterine relapse is an uncommon occurrence in ALL, and there is currently no established therapeutic approach. This rare presentation may be more common with newer immunotherapeutic approaches in patients with advanced disease and should be considered in the presence of metrorrhagia or pain. Although CAR T-cell therapy may be effective in extramedullary disease, hysterectomy may be a viable option in the treatment of uterine relapse in ALL to manage gynaecological symptoms and reduce tumour burden in order to achieve a complete response to systemic treatment.

Keywords

Extramedullary relapse; Gynaecological organs; B-cell acute lymphoblastic leukaemia; CAR T-cell therapy; Methrorragia; Hysterectomy

1. Introduction

Acute lymphoblastic leukaemia (ALL) is the most prevalent malignant disease in paediatric patients [1], with an over 85% survival rate. Notwithstanding recent advances in medical treatment, relapse of ALL occurs in 15–20% of patients [2]. The prognosis for these children is frequently unfavourable, representing a significant contributor to cancer-related mortality in this patient group. Extramedullary relapse of ALL in gynaecological organs is exceedingly rare, with the majority of cases documented involving the ovary [3]. This report presents a case of a 14-year-old female with an extramedullary relapse of B-cell acute lymphoblastic leukaemia (B-ALL) in the uterus, presenting with symptoms of abnormal uterine bleeding and severe pelvic pain.

2. Case report

A 14-year-old female with no personal or family history of interest was diagnosed with B-ALL in July 2023 following a clinical presentation of back pain, headache and fever that had persisted for two days. The patient's white blood cell count was 24.6 $\times$ 10^9/L. No evidence of central nervous system (CNS) infiltration, mediastinal mass or extramedullary disease at other levels was observed. Genetic studies revealed the absence of primary recurrent genetic alterations in ALL, thus classifying the disease as B-cell other acute lymphoblastic leukaemia (B-other ALL). Fluorescence *in situ* hybridisation (FISH) identified an immunoglobulin heavy locus (IgH) gene rearrangement (the partner gene was not identified), while next generation sequencing (NGS) revealed a Kirsten

rat sarcoma viral oncogene homologue *(KRAS)* mutation. She was treated in accordance with the Spanish national protocol (SEHOP-PETHEMA-2013) for high-risk patients, which comprises four-drug induction, consolidation, delayed intensification and maintenance. Bone marrow assessment showed 9% blasts by morphology with measurable residual disease (MRD) positivity by flow cytometry (0.11%) and by polymerase chain reaction (PCR) (0.35%) at the end of IA induction, reaching complete remission at the end of IB induction with MRD positivity but below 0.01% by both techniques.

Six months after initial diagnosis, after completing block 3 of intensive polychemotherapy (AR-3 regimen), she was diagnosed with early relapse of B-ALL in the bone marrow with cluster of differentiation 19 (CD19) and CD22 expression. No new genetic alterations were found in the studies performed at relapse (FISH, NGS). She was considered a candidate for chimeric antigen receptor (CAR) T-cell therapy targeting CD19 (CAR-T19). She was enrolled in the CART19BE-03Ped clinical trial (ARI-0001®, co-stimulatory domain 4-1BB) as a high-risk first relapse. Leukapheresis was performed without incident and an adequate product was obtained. While waiting for the CAR-T19 cells to be manufactured, she received inotuzumab as a bridging treatment. Three doses (at 0.8, 5 and 0.5 mg/m^2) were administered without drug-related complications. However, after the first dose of inotuzumab, she developed severe painful metrorrhagia resembling menstruation. She was treated with chorionic gonadotropin analogue (gonapeptyl) and antifibrinolytics. Serial ultrasound scans showed homogeneous endometrial thickening and numerous large clots. Despite treatment, metrorrhagia persisted with high transfusion requirements and oral progestogens were started with partial response. An abdominopelvic magnetic resonance imaging (MRI) scan was performed (Fig. 1), which showed heterogeneous thickening of the entire uterine wall, with a dilated myometrium occupied by an infiltrative, hypointense lesion with areas of high diffusion restriction, suggesting leukaemic infiltration. 18-Fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG-PET/CT) was also performed, showing intense uterine hypermetabolism (Standardized Uptake Value (SUV) max 11.8) and evidence of peritoneal/mesenteric infiltration (Fig. 2). Hysteroscopy was performed and endometrial biopsies showed infiltration by B lymphoblasts with CD19 and CD22 expression by flow cytometry, with negative CD20 and surface immunoglobulin expression. A bone marrow aspirate was performed on day +22 of the inotuzumab cycle and showed morphological remission with MRD of 0.3% leukaemic cells CD19+/CD22.

Following the diagnosis of a second extramedullary uterine and peritoneal relapse of chemorefractory B-ALL, a multidisciplinary committee (oncology, surgery and gynaecology teams) discussed and agreed to perform a bilateral hysterosalpingo-oophorectomy followed by CAR-T19 therapy and, if a complete remission was achieved, to consolidate the response with a subsequent haematopoietic stem cell transplantation (HSCT). The surgery was performed laparoscopically. Macroscopically, an enlarged uterus was seen with nodular whitish-pink lesions overlying the bladder peritoneum, from which biopsies were taken (Fig. 3). No peritoneal implants were visualised macroscopically. She had a vaginal tear which required two sutures. The postoperative course was favourable with no complications. Pathology showed extensive diffuse blastic infiltration of the uterine body, sparing the cervix, but also involving both fallopian tubes, ovaries and peritoneal bladder biopsies. Immunohistochemically, the blastic proliferation was positive for paired box 5 (*PAX5*), CD10 and CD22, virtually negative for CD19 and negative for CD20 and surface immunoglobulin expression (Fig. 4). Flow cytometry showed a majority population with CD19+ and CD22 expression and a CD22 negative subpopulation (7%) with negative CD20 and surface immunoglobulin expression. The peritoneal fluid was negative for malignant cells. Bone marrow assessment was performed at this time, showing an MRD of 0.13% on bone marrow aspirate, but a patchy infiltration of approximately 25% blasts with CD19+ expression and heterogeneous CD22 expression on bone marrow biopsy.

After 7 days of postoperative recovery, lymphodepleting chemotherapy (fludarabine 30 mg/m^2/day, 3 doses and cyclophosphamide 300 mg/m^2/day, 3 doses) was administered followed by CAR-T19 cell infusion (ARI-0001). She received a total of 3×10^6 CAR-T cells/kg fractionated into 4 aliquots (0.1, 0.3, 0.6 and 2×10^6 CAR-T19 cells/kg). Prior to the ARI-0001 cell infusion, she had a high tumour burden (25% blasts in bone marrow biopsy) without CNS infiltration or extramedullary disease elsewhere. She presented with grade 2 cytokine release syndrome (CRS) 24 hours after the 3rd fraction infusion, which was treated with two doses of tocilizumab, methylprednisolone for 4 days and supportive care in the paediatric intensive care unit for 24 hours; she did not receive inotropes nor oxygen therapy. She associated analytical changes suggestive of macrophage activation with elevated bilirubin, ferritin and hypofibrinogenemia. She had no neurotoxicity. She developed B-cell aplasia and CAR-T19 cells were detected in peripheral blood by flow cytometry.

Response assessment one month after CAR T-cell therapy showed no evidence of leukaemic infiltration in the bone marrow (BM) with negative MRD, but extramedullary involvement could not be excluded. The 18F-FDG PET/CT scan showed evidence of diffuse hypermetabolism of the peritoneum, which may represent a pseudo-progression of the disease. Given the clinical improvement of the patient, who was asymptomatic at the time and had no evidence of disease in the BM, it was decided to repeat the 18F-FDG PET/CT in one month. The 18F-FDG PET/CT remained stable for two months after CAR-T19 infusion. However, an MRD of 0.0038% CD19++/CD22−/+ (17%) was detected in the BM. A laparoscopic peritoneal biopsy was performed to exclude extramedullary infiltration prior to HSCT. Macroscopically, a thickened peritoneum with an infiltrative aspect and haemorrhagic peritoneal fluid was visualised. Three nodular lesions (periumbilical, left flank and left iliac fossa) were subjected to biopsy. The pathological anatomy confirmed peritoneal infiltration by B-ALL, with CD19 expression by both immunohistochemistry and flow cytometry being CD22 negative.

Given the refractoriness of the disease to both chemotherapy and immunotherapy (CAR-T19 and inotuzumab) and the rapid

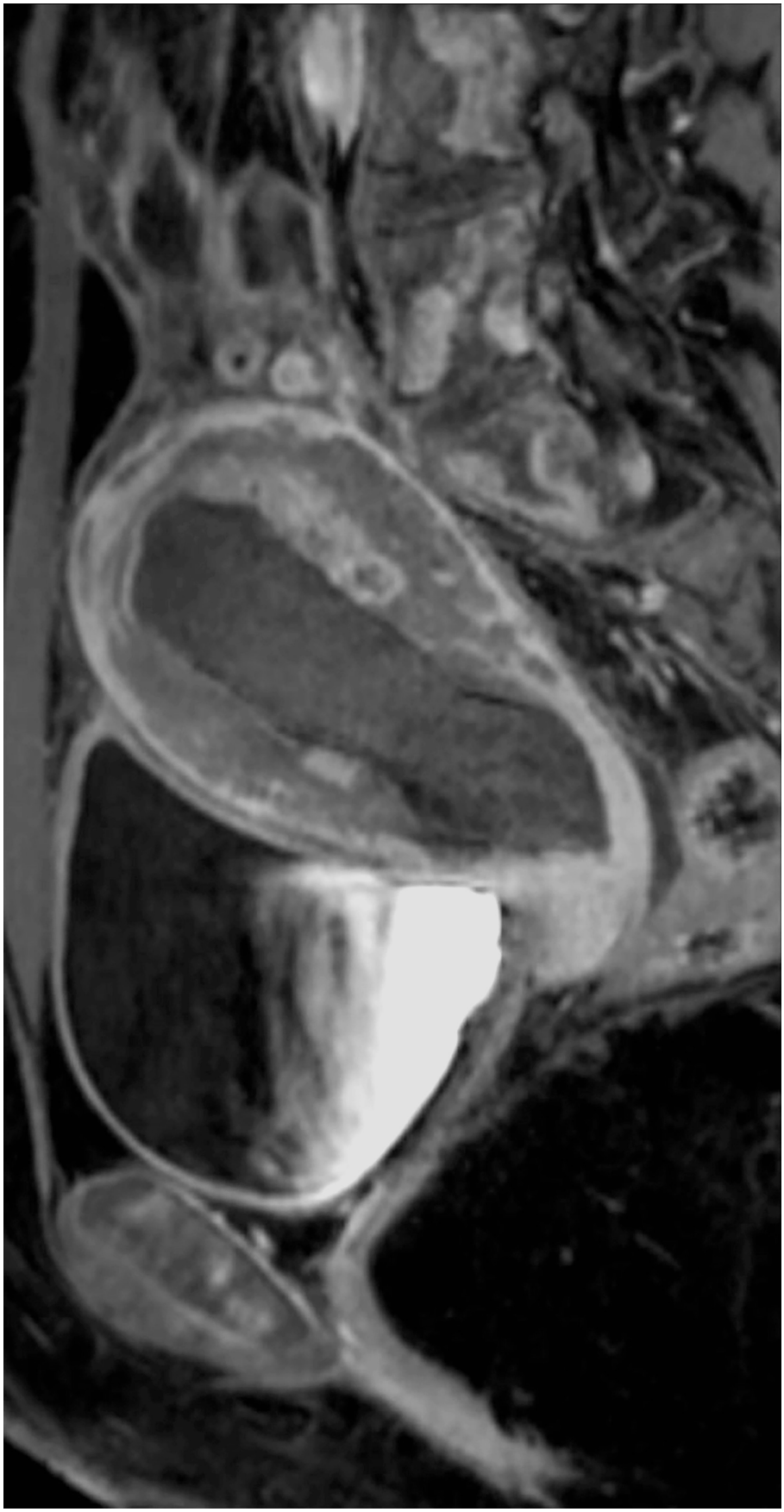

FIGURE 1. Abdomino-pelvic MRI. Sagittal T1 contrast-enhanced section which showed heterogeneous thickening of the entire uterine wall, identifying a widened myometrium occupied by a hypointense infiltrative lesion suggestive of leukaemic infiltration.

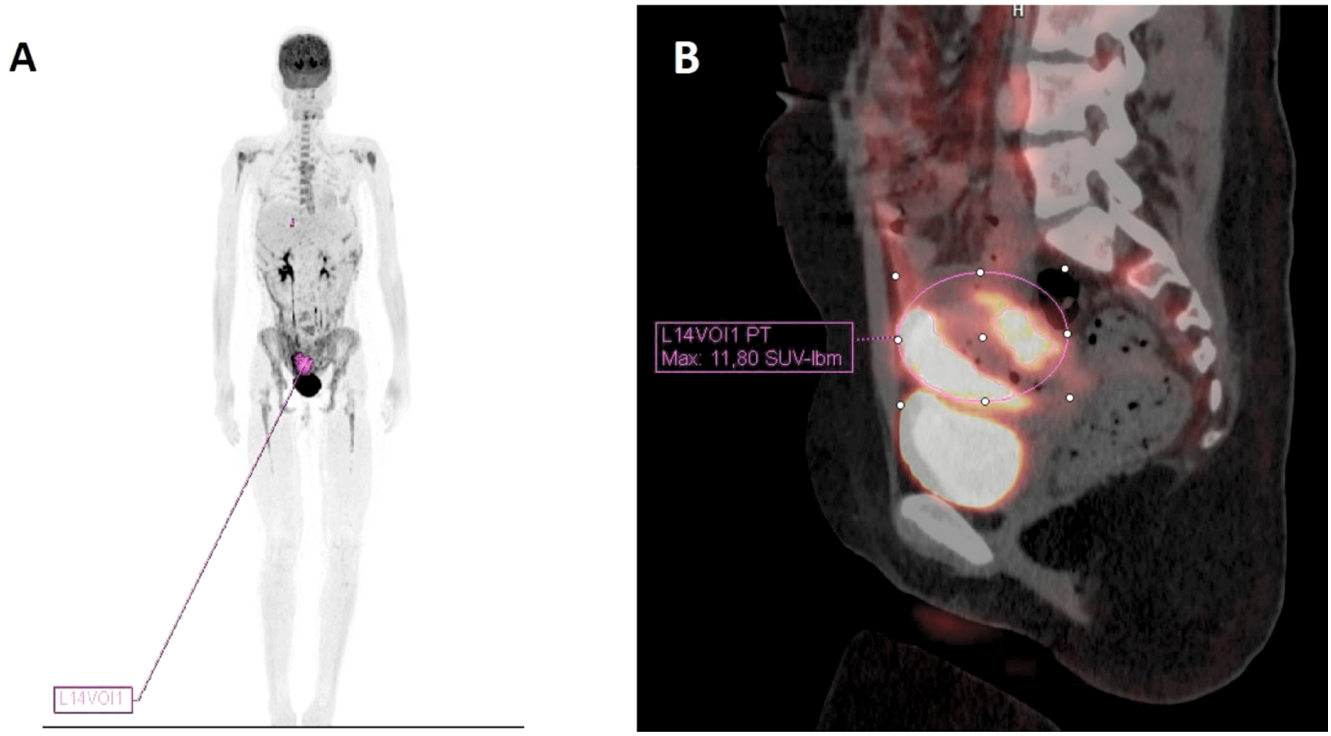

FIGURE 2. 18-Fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG-PET/CT). (A) Coronal section showing increased metabolism in uterus, moderate/intense diffuse increase in osteomedullary glycaemic metabolism suggestive of infiltration and signs of peritoneal/mesenteric infiltration predominantly in the perihepatic and perihepatic region. (B) Sagittal section showing an enlarged uterus with heterogeneous thickening of the entire wall and associated intense glycaemic hypermetabolism, predominantly inferior with Standardized Uptake Value (SUV) max 11.8. SUV: Standardized Uptake Value.

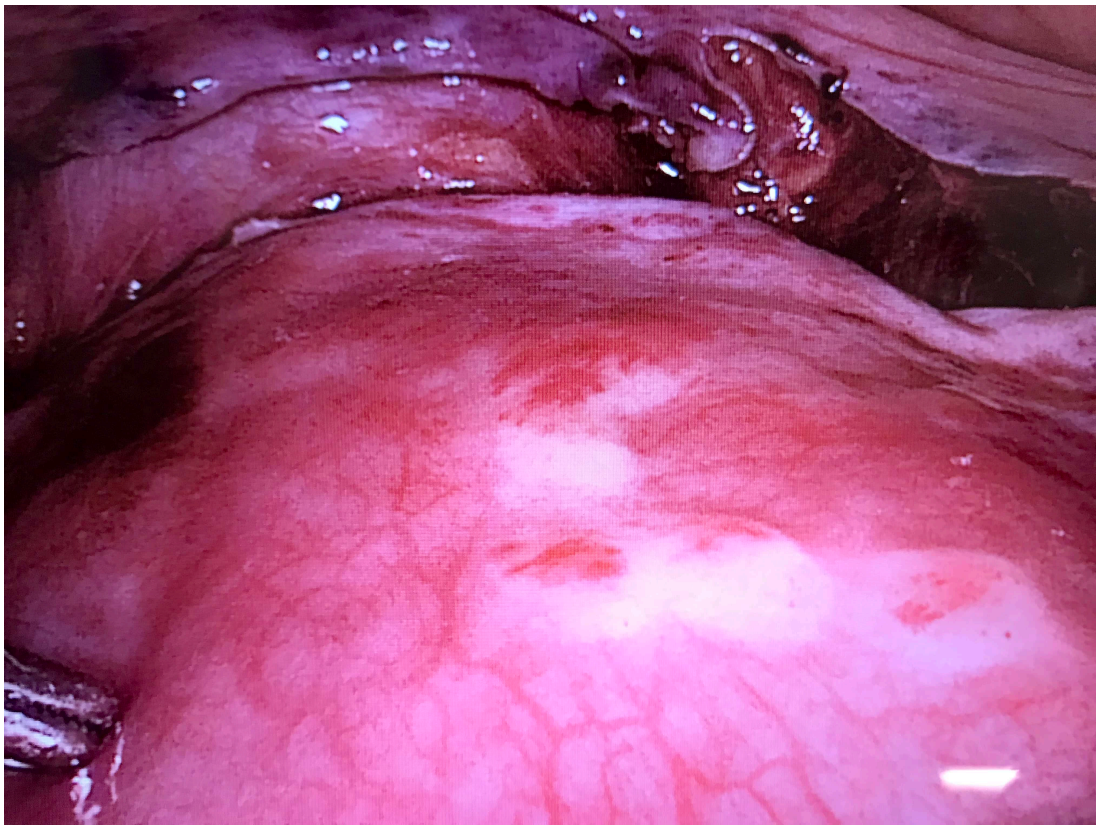

FIGURE 3. Laparoscopic vision of the uterus and bladder peritoneum with clear signs of leukemic infiltration.

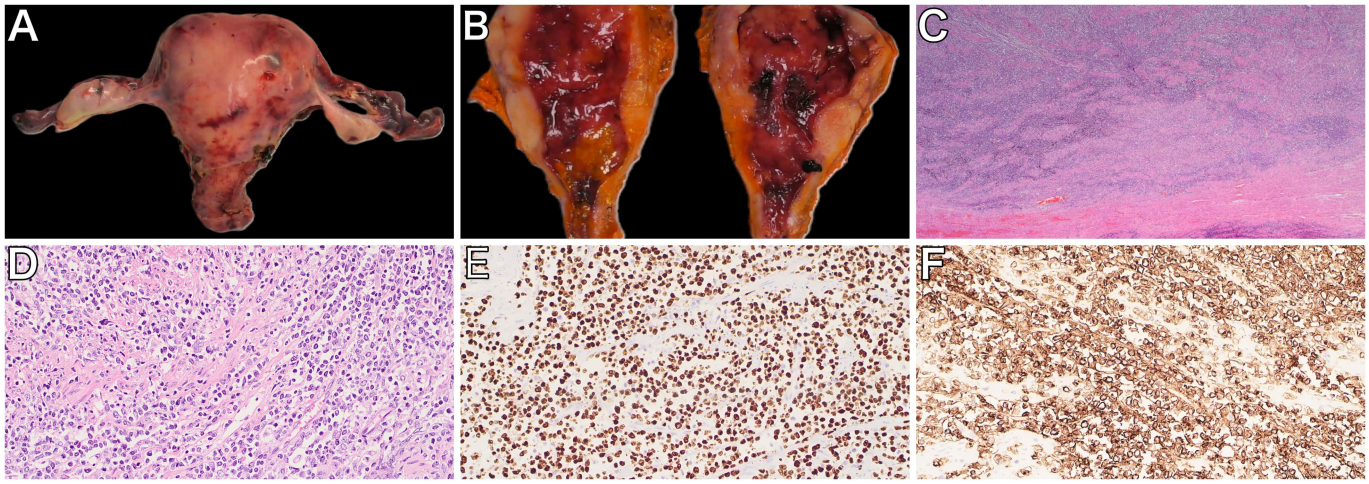

FIGURE 4. Pathology results. (A) Hysterectomy and bilateral salpingo-oophorectomy. (B) Open uterus after removing intraluminal blood, showing thickened myometrium with white ill-circumscribed lesions. Microscopic photographs showing diffuse blastic infiltration of the myometrium (HE ×4 (C), HE ×40 (D)) with immunoexpression of PAX5 (×40) (E) and CD10 (×40) (F).

disease progression, the possibility of receiving HSCT or other treatments with curative intent was discouraged and initiated follow-up also by the palliative care team. The patient died of disease progression four months after CAR-T19 cell infusion.

3. Discussion

Extramedullary relapse of leukaemia occurs in 2–6% of cases, with the most frequent sites being the CNS and the testes [2]. The advent of new immunotherapeutic agents, in particular inotuzumab and blinatumomab, may potentially alter the conventional pattern of relapse, with an increased incidence of extramedullary locations. Leukaemic ovarian involvement has been documented in numerous autopsy series, with an incidence ranging from 11 to 50% in patients with BM relapse. However, it has only rarely been observed during the clinical course of leukaemia [3]. Moreover, uterine involvement is an exceedingly rare occurrence. A recent publication [4] has identified six cases, one of which was located in the cervix [5]. The initial indications of uterine recurrence are vaginal bleeding and/or pelvic discomfort [2, 4]. However, these are frequently observed symptoms of hormonal imbalances that are commonly seen in adolescents and perimenopausal women. The most common methods of menstrual suppression include combined hormonal contraceptives, progestin-only therapy and gonadotropin-releasing hormone agonist, each of which has been demonstrated to be effective in inducing amenorrhea. In the case of our patient, both symptoms (heavy menstrual bleeding and severe pelvic pain) were present, yet there was no response to hormonal suppressive treatment. Serial gynaecological ultrasounds were performed, yet no evidence of possible uterine infiltration by leukaemia was identified. However, MRI can be of significant value in differentiating uterine involvement due to leukaemia from other benign uterine changes, such as leiomyoma, adenomyosis or primary uterine cancer [6, 7]. In the event of uterine relapse of ALL, MRI demonstrates high intensity on T2-weighted images with gadolinium enhancement and a reduction in the apparent diffusion coefficient (ADC) [8, 9], as observed in our case. Additionally, 18F-FDG-PET/CT is a valuable supplementary examination in instances of suspected uterine recurrence and to exclude other potential sites of recurrence. However, it does not permit differentiation from other entities, such as infection. In many cases, as in that of our patient, a biopsy is necessary to confirm the diagnostic suspicion of tumor infiltration.

In cases where uterine involvement is suspected, a biopsy is essential for confirming the recurrence. In this case, hysteroscopy with biopsy was performed to confirm the diagnosis. This is a minimally invasive surgical procedure that has been described in other cases in the literature [2].

Uterine recurrence is a rare occurrence in ALL, and as a result, there is currently no established standard of care. It has been demonstrated that CAR T-cell therapy is capable of more effective penetration of extramedullary sites. However, it is important to note that, as with HSCT, the possibility of relapse remains. The use of CAR-T19 therapy, specifically ARI-001 cells [10], has demonstrated efficacy in the treatment of relapsed/refractory (R/R) B-ALL patients presenting with isolated extramedullary infiltration. A further case, documented in the literature, describes the treatment of a young adolescent with a painful condition known as metrorrhagia. In this instance, the patient underwent a hysterectomy [2]. However, in this case, there was no evidence of tumour infiltration of the uterus on histological examination. The decision to perform a hysterosalpingo-oophorectomy on this 14-year-old patient was not taken lightly. The primary objective of the care team was to reduce the risk of recurrence of leukaemia, to reduce the tumour burden and to attempt to achieve complete remission following CAR-T19 therapy. The decision to proceed with an adnexectomy was made on the grounds that aggressive chemotherapy and HSCT would undoubtedly compromise ovarian function. Additionally, imaging tests (18F-FDG-PET/CT) indicated a high probability of ovarian infiltration, suggestive of peritoneal involvement. In the case of our patient, a laparoscopic hysterectomy with double adnexectomy was performed without complications, after which

CAR-T19 therapy was initiated a few days later. Another case described in the literature did not present any complications [2]. A review of the literature revealed no instances of laparoscopy being used to confirm extramedullary peritoneal involvement as was done in our case. This minimally invasive procedure enabled us to confirm the recurrence of the disease through peritoneal biopsy and modify the therapeutic plan, as consolidation with HSCT is contraindicated in this situation. It is crucial to emphasise the ovarian involvement in our case, as it is imperative to screen ovarian tissue for leukemic cells prior to ovarian tissue cryopreservation, as proposed by other authors [11].

In conclusion, we present a case of uterine involvement by B-ALL, an unusual site of extramedullary involvement. This rare presentation may be observed with greater frequency in patients with advanced disease undergoing newer immunotherapeutic approaches and should be considered in the presence of metrorrhagia or pain. While CAR T-cell therapy may prove effective in extramedullary disease, hysterectomy may be a viable option for the treatment of uterine relapse in ALL, to address gynaecological symptoms (metrorrhagia or pain) and reduce tumour burden, thereby achieving a complete response with systemic treatment. The limitation of this study is that it is a case report, and other cases of uterine involvement in leukaemia need to be analysed to confirm our conclusions.

AVAILABILITY OF DATA AND MATERIALS

We present all data available in the text and photos of the manuscript.

AUTHOR CONTRIBUTIONS

SGN, CS, AAS, JLDD, MT, EL and SM—provided help and advice on elaboration of the manuscript. EGB, NSS, SR and SP—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved of the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The parents of the patient and the patient give their consent for the publication of this article. The Drug Research Ethics Committee of the Fundació Sant Joan de Déu has evaluated the article on the clinical case received and does not observe any ethical inconvenience for its presentation. Approval number: CEIm ART-04-24.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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