

·CASE ANALYSIS·

·临床病例讨论·

急性淋巴细胞白血病移植术后子宫及卵巢复发1例

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[摘要] 急性淋巴细胞白血病(acute lymphoblastic leukemia, ALL)是一种常见的急性白血病, 本质为造血干细胞的恶性克隆性增殖性疾病。目前, 异基因造血干细胞移植(allogeneic hematopoietic stem cell transplantation, allo-HSCT)的广泛应用显著提高了患者的生存率, 已成为ALL最有效的治疗手段。然而, 移植术后仍存在复发风险, 其中以髓内复发为主, 髓外复发相对少见, 而女性生殖系统的髓外复发尤为罕见。本文报道1例allo-HSCT术后发生子宫及卵巢复发的ALL患者, 经盆腔包块穿刺活检确诊为髓外复发。后续给予化疗、放疗及嵌合抗原受体T细胞免疫疗法(chimeric antigen receptor T-cell immunotherapy, CAR-T)联合治疗, 子宫及卵巢肿物完全消退, 达到临床治愈。值得注意的是, 急性白血病移植术后生殖系统复发易被误诊为生殖系统原发恶性肿瘤, 因此, 正确鉴别原发与继发性肿瘤, 尽早实施有效治疗至关重要。临床实践中应结合患者病史及MRI影像学特征, 提高诊断准确性, 从而避免不必要的手术创伤, 改善患者长期预后。

[关键词] 急性淋巴细胞白血病; 异基因造血干细胞移植; 髓外复发; 生殖系统恶性肿瘤; 继发性肿瘤

Uterine and ovarian relapse of acute lymphoblastic leukemia after transplantation: A case report

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is a common type of acute leukemia and is essentially a malignant clonal proliferative disorder of hematopoietic stem cells. Currently, the widespread application of high-dose chemotherapy combined with allogeneic hematopoietic stem cell transplantation (allo-HSCT) has significantly improved patient survival and has become the most effective therapeutic strategy for ALL. However, relapse remains a major challenge after transplantation. Most relapses occur in the bone marrow, whereas extramedullary relapse is relatively uncommon, and relapse involving the female reproductive system is extremely rare. Herein, we report a case of ALL with uterine and ovarian relapse after allo-HSCT. Extramedullary relapse was confirmed by pelvic mass

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biopsy. The patient subsequently received combined treatment with chemotherapy, radiotherapy, and chimeric antigen receptor T-cell (CAR-T) immunotherapy, resulting in complete regression of the uterine and ovarian lesions and achieving clinical remission. It should be noted that relapse of acute leukemia in the reproductive system after transplantation can be easily misdiagnosed as a primary malignancy of the reproductive system. Therefore, accurate differentiation between primary and secondary tumors and early initiation of effective treatment are essential. In clinical practice, diagnostic accuracy should be improved by integrating the patient's clinical history with magnetic resonance imaging (MRI) findings, thereby avoiding unnecessary surgical trauma and improving long-term prognosis.

KEY WORDS acute lymphoblastic leukemia; allogeneic hematopoietic stem cell transplantation; extramedullary relapse; malignant tumors of the reproductive system; secondary tumor

急性淋巴细胞白血病(acute lymphoblastic leukemia, ALL)是一种常见的急性白血病,属于造血干细胞的恶性增殖性疾病。目前,高剂量化疗仍是其基础治疗手段,而异基因造血干细胞移植(allogeneic hematopoietic stem cell transplantation, allo-HSCT)的广泛应用显著提高了患者的生存率,被认为是ALL最有效的治疗方式。然而,仍有20%~40%的ALL患者在allo-HSCT后出现复发,导致治疗失败^[1-3]。根据复发部位,可分为髓内复发、髓外复发及二者并存的情况,其中髓外复发通常提示预后不良,治疗难度较大^[4]。髓外复发的常见部位包括中枢神经系统、淋巴结和睾丸^[5],而以女性生殖系统为首发表现者极为罕见。本文报告1例ALL移植术后以盆腔肿块为首发表现,最终确诊为子宫及卵巢复发并再次治疗成功的病例。

1 病例资料

患者,女,48岁,2021年6月3日因“B超发现盆腔肿块2月”就诊于中南大学湘雅三医院。既往于2020年因ALL行allo-HSCT,术后复查随访认为临床治愈。

妇科检查:子宫增大如孕4月大小,质中,无压痛;子宫右上方可扪及约3 cm结节状肿块,双侧附件区扪及欠满意。三合诊:子宫直肠窝未触及片状结节,退指无染血。实验室检查:人乳头瘤病毒(human papilloma virus, HPV)52、58型阳性,液基细胞学检测(thinprep cytologic test, TCT)提示无明确

意义的非典型鳞状细胞(atypical squamous cells of undetermined significance, ASC-US);阴道镜活检示慢性炎症。肿瘤标志物:糖类抗原(carbohydrate antigen, CA)125为54.29 U/mL(正常参考值:<35 U/mL),CA199为47.48 U/mL(正常参考值:<34 U/mL),癌胚抗原(carcinoembryonic antigen, CEA)为14.56 ng/mL(正常参考值:<4.7 ng/mL),甲胎蛋白(alpha-fetoprotein, AFP)为阴性。外周血常规:血红蛋白为90 g/L,红细胞计数为 $3.37 \times 10^{12}/L$ 。骨髓穿刺活检未见异常细胞;脑脊液常规及生化检查均未见异常。

妇科B超示:宫颈中段延续至盆腔一大小约109 mm×103 mm×105 mm的以低回声为主的混合性包块;左、右附件区混合回声包块,大小分别约为86 mm×60 mm、71 mm×54 mm,形态不规则,边界不清,考虑盆腔转移性肿瘤。盆腔MRI(图1、2)显示:子宫肌层内多发结节状、不规则条带状稍长 T_1 稍长 T_2 信号肿块,边界清晰,弥散加权成像(diffusion-weighted imaging, DWI)呈高信号,表观弥散系数(apparent diffusion coefficient, ADC)图呈低信号,增强后呈不均匀轻中度强化;双侧宫旁及下腹部多发类似信号的不规则肿块,彼此相连,其中较大者位于右侧附件区,横截面约46 mm×40 mm,其内下方似与子宫右侧壁相连,考虑恶性肿瘤(子宫肉瘤伴转移可能)。胃镜示胃多发息肉及慢性非萎缩性胃炎;(胃底、胃体)活检组织见息肉样生长,间质水肿,局灶大量淋巴样组织增生伴非典型增生,结合临床病史,考虑白血病累及胃黏膜。

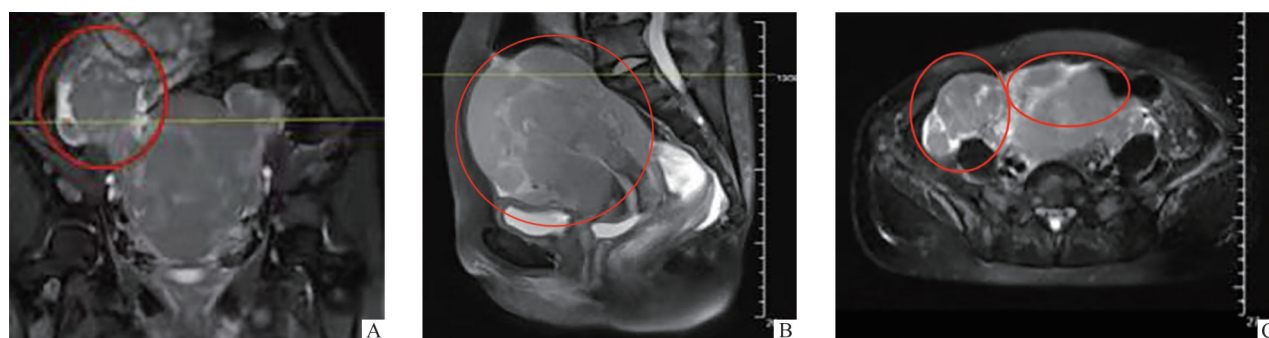


图1 移植后复发MRI图像(2021年6月5日)

Figure 1 MRI image of recurrence after transplantation (June 5, 2021)

A–C: Coronal (A), sagittal (B) and transverse (C) MRI images of patients with recurrent uterus and ovary after transplantation.

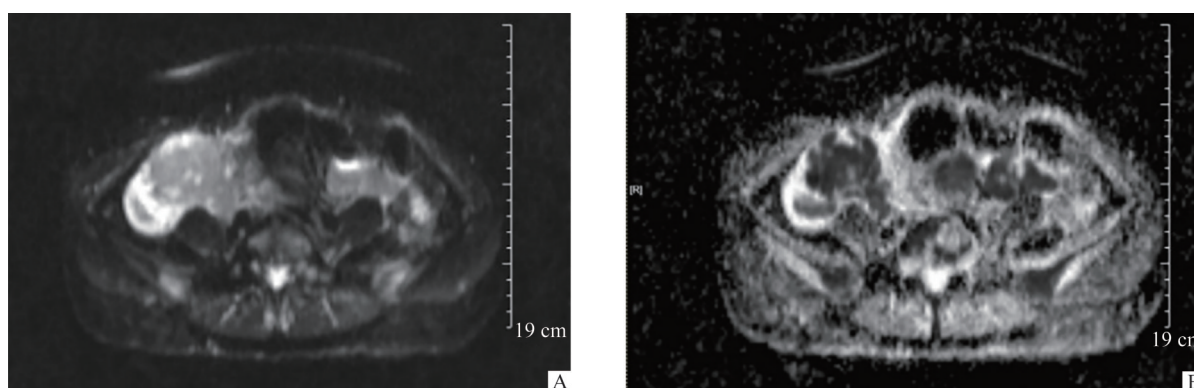


图2 移植后复发弥散加权成像及表观弥散系数图像(2021年6月5日)

Figure 2 Diffusion-weighted imaging and apparent diffusion coefficient images of recurrence after transplantation (June 5, 2021)

A: Diffusion-weighted imaging shows high signal. B: Apparent diffusion coefficient image shows low signal. The tumor may be malignant.

行B超引导下盆腔包块穿刺活检,病理结果(图3):圆形细胞肿瘤,肿瘤细胞异型明显,呈穿插性生长于肌肉组织间。免疫组织化学(图4):分化簇(cluster of differentiation, CD)19(+), CD20(+++), CD22(弱+), CD43(+), CD99(+), 白细胞共同抗原(leukocyte common antigen, LCA)(+), 白细胞雌激素受体(leukocyte estrogen receptor, LER)(++), 末端脱氧核苷酸转移酶(terminal deoxynucleotidyl transferase, TdT)(少数阳性), Epstein-Barr病毒编码的小RNA(Epstein-Barr virus encoded RNAs, EBER)对照(+), CD3、CD5、CD23、CD34、CD117、广谱细胞角蛋白(cytokeratin pan, CKpan)、细胞周期蛋白D1、EBER、髓过氧化物酶(myeloperoxidase, MPO)均为阴性, Ki-67增殖指数约80%。病理诊断: B细胞源性淋巴造血系统恶性肿瘤, 结合病史, 考虑白血病复发。全腹CT提示盆腔子宫、双肾、肝脏、右侧肾

上腺、胰腺多发病变, 考虑白血病并多发脏器浸润可能。

经多学科会诊(multi-disciplinary treatment, MDT), 考虑为ALL移植术后子宫及卵巢复发合并多发脏器浸润(髓外复发)。遂予综合治疗: 先后行3次利妥昔单抗方案[第1次: 利妥昔单抗注射液600 mg; 第2次: 利妥昔单抗550 mg(第1天)+多柔比星脂质体注射液20 mg(第2天); 第3次: 利妥昔单抗550 mg], 联合25次放疗及嵌合抗原受体T细胞免疫疗法(chimeric antigen receptor T-cell immunotherapy, CAR-T)。治疗后于2023年11月1日复查盆腔MRI: 子宫大小形态正常, 未见明显异常信号及强化; 双附件区未见肿块影(图5)。2024年6月20日正电子发射计算机断层显像仪(positron emission tomography and computed tomography, PET/CT): 全身未见明确恶性肿瘤病变征象(图6)。肿瘤标志物(CA125、

CA199、CEA)均转阴。临床判定为ALL移植术后子宫及卵巢复发病灶治愈。随访15个月(2023年11月1日至2025年2月1日),无复发迹象。

本研究已获得患者的知情同意并获得中南大学湘雅三医院伦理委员会伦理审查批准(审批号:快25088)。

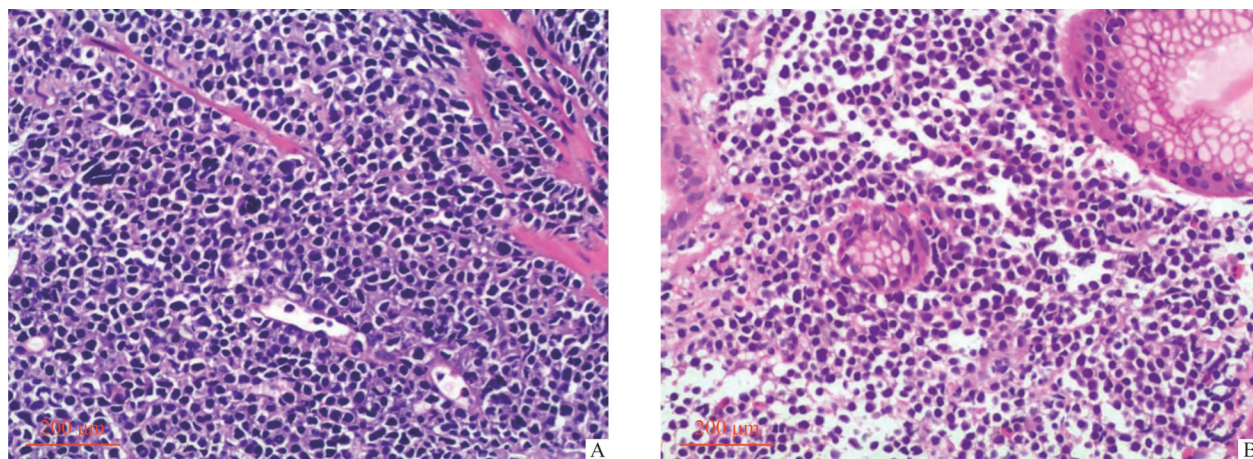


图3 移植后髓外复发病理结果(HE染色)

Figure 3 Pathological results of extramedullary recurrence after transplantation (HE staining)

A: Pelvic mass puncture; B: Fundus stomach body. HE: Hematoxylin and eosin.

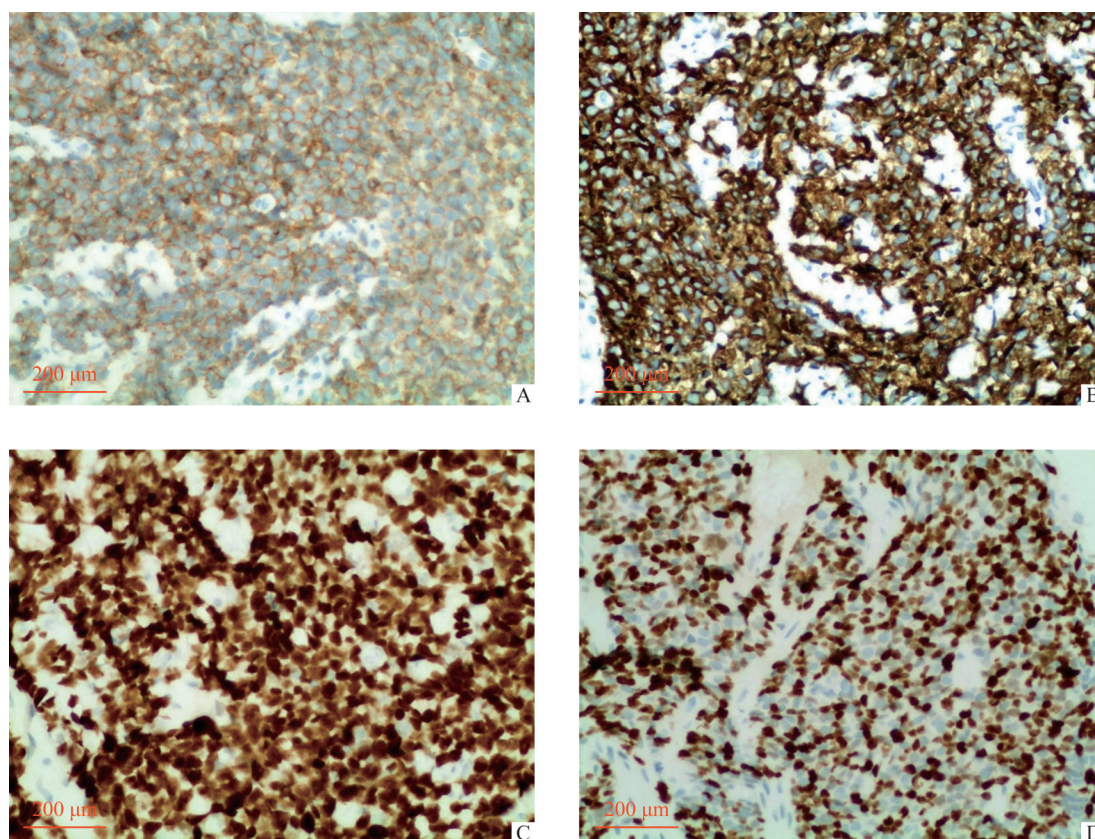


图4 移植后髓外复发免疫组织化学结果

Figure 4 Immunohistochemical results of extramedullary recurrence after transplantation

A: Positive expression for CD19; B: Positive expression for CD20; C: Positive expression for lymphoid enhancer factor-1; D: Ki-67 proliferation index is about 80%.

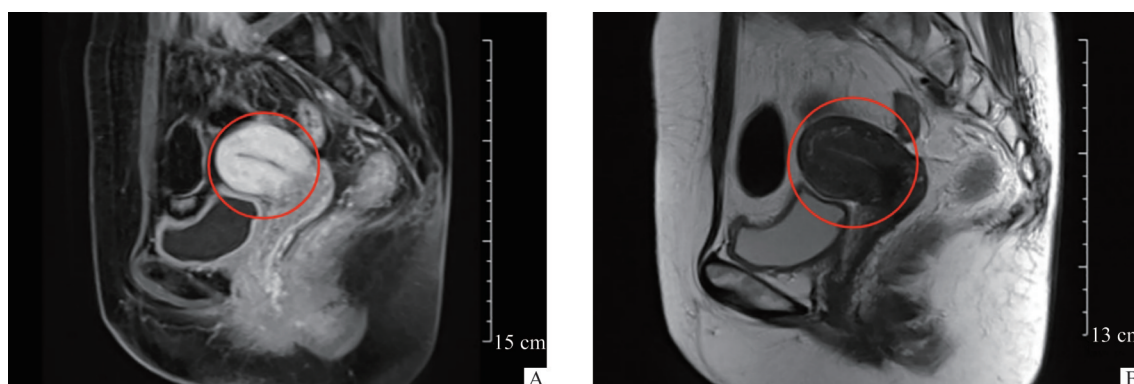


图5 移植后复发患者MRI矢状位 T_1 加权成像、 T_2 加权成像图像(2023年11月1日)

Figure 5 MRI sagittal T_1 -weighted imaging and T_2 -weighted imaging images of patients with recurrence after transplantation (November 1, 2023)

A: T_1 WI; B: T_2 WI. MRI images of patients with recurrent uterus and ovaries after transplantation show the disappearance of tumors in the uterus and bilateral ovarian regions.

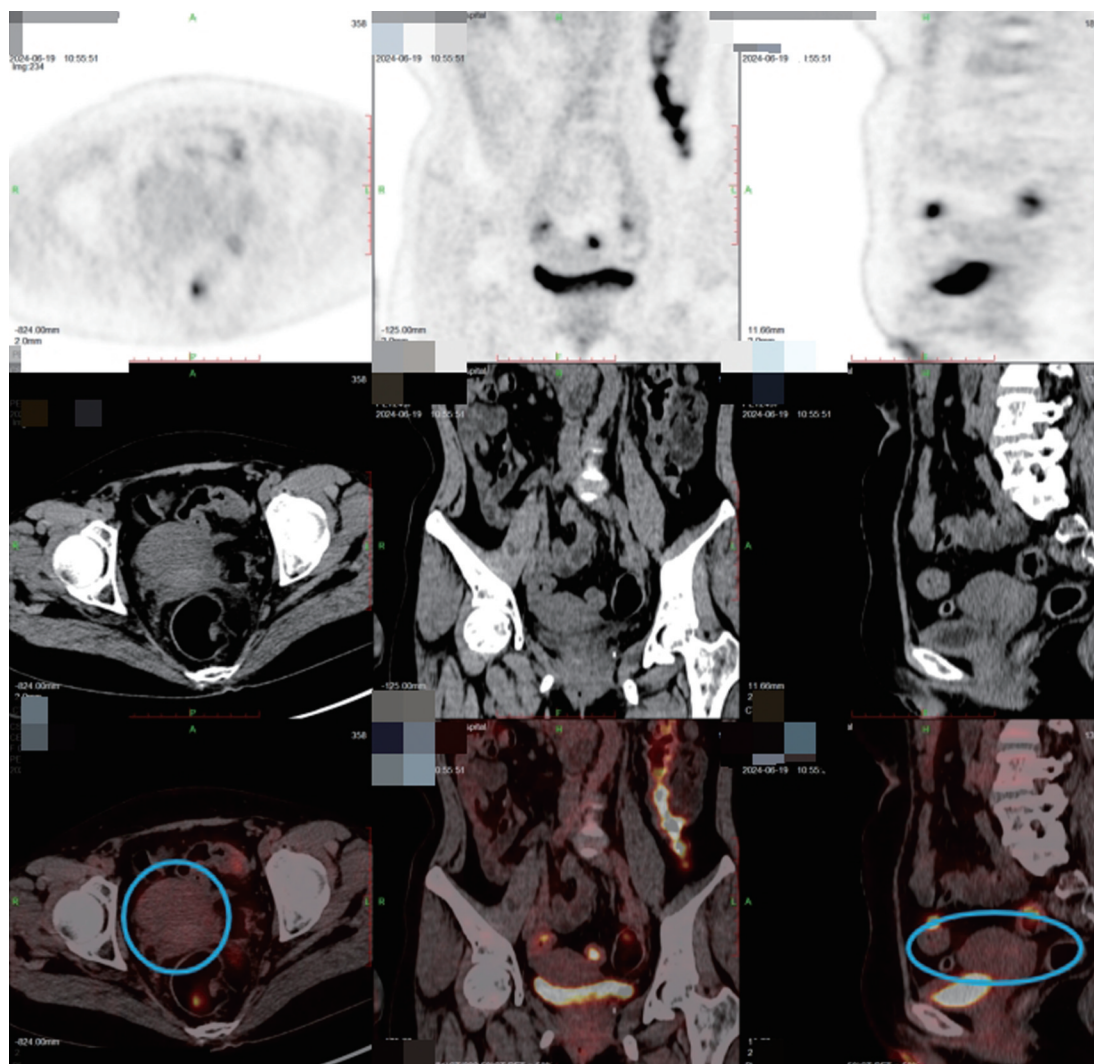


图6 移植后复发患者PET-CT图像(2024年6月20日)未见明显恶性肿瘤迹象

Figure 6 PET-CT images of patients with recurrence after transplantation (June 20, 2024) showing no obvious signs of malignant tumors

PET/CT: Positron emission tomography and computed tomography.

2 讨论

75%~89%的成人ALL经过规范治疗可获得完全缓解(complete remission, CR),但缓解后的复发率较高,临床病死率也高,大部分移植后复发患者生存结局差,最终因疾病进展而死亡,5年生存率仅为40%~45%^[6-7],所以成人复发ALL的治疗极具挑战。ALL治疗后按照复发部位,可分为髓内复发、髓外复发和髓内伴髓外复发,其中髓外复发是一种特殊的复发类型^[8],可累及全身多个组织器官,多发于中枢神经系统(central nervous system, CNS)、淋巴结、皮肤、眼部、睾丸等。CNS是ALL髓外复发最重要的部位,CNS白血病表现可能不典型^[9],通常表现为颅内压增高(头痛、视盘水肿、意识障碍)、脑膜刺激征(颈项强直、Kernig征及Brudzinski征阳性)、神经功能缺损症状(视力障碍、肢体运动障碍、感觉异常、尿便障碍)、脑脊液异常(脑脊液压力升高、细胞数增多、生化改变)等。睾丸是男性ALL患者髓外复发可能涉及的部位,通常表现为单侧或双侧睾丸无痛性肿大,质地较硬,可伴有轻压痛。而宫颈及女性生殖器官罕见ALL髓外复发^[10]。

由于发生在女性生殖系统的髓外复发较为罕见,并且无特异性症状出现,诊断较为困难,极易误诊,从而延误治疗。如误诊后选择手术会增加患者负担,影响预后。MRI由于具有多方位、多序列、多参数成像等特点,可用于区分癌症与良性疾病、分期和评估治疗反应^[11],在妇科疾病诊断中发挥着重要作用。本例患者因“盆腔包块”入住妇科。入院时MRI见子宫及双附件区多发不规则肿块影,彼此相连,结合DWI呈高信号,ADC图呈低信号判断肿块可能是生殖系统恶性肿瘤性病变。经过分析病史及结合妇科检查、MRI影像分析及盆腔包块穿刺活检诊断为ALL骨髓移植后子宫及卵巢复发(髓外复发)。目前关于复发性ALL尚无统一的治疗意见,建议是诱导CR后尽快行allo-HSCT; CAR-T联合allo-HSCT也是一种治疗选择。在用CAR-T获得CR的复发性ALL患者中,allo-HSCT可以明显延长这部分患者的无病生存期^[6]。Jacoby等^[12]报告了1例复发性ALL累及卵巢的患者,通过CAR-T治疗获得CR。Kim等^[13]报告,1例ALL患者经剖腹探查明确卵巢孤立性髓外复发,经CCG 1882方案完成全身再诱导化疗,达到完全缓解,在随访的4个月内未发现复发或转移的证据。目前没有针对allo-HSCT后髓外复发的既定指南,但全身化疗、重复allo-HSCT、供者淋巴细胞输注和局灶性放疗可能有效。本病例中该患者经过规范的血液科综合抗肿瘤治疗,包括3次利妥昔单抗治

疗、25次放疗、CAR-T治疗后子宫及双侧卵巢区复发病灶消失,随访至今无其他部位复发证据,考虑再次无病生存。

子宫及卵巢的髓外复发是罕见的发生于生殖系统的血液系统恶性肿瘤,虽为局部病灶,但被视为全身疾病的局部表现,其治疗不同于生殖系统原发肿瘤的以手术为主的综合治疗,而是以全身化疗为主的治疗。虽然生殖系统复发在女性ALL患者中并不常见,但随着联合化疗患者生存时间的延长,生殖系统复发可能成为一个需要重视的问题。故而,在患者既往有血液系统恶性肿瘤治疗史等情况时,需要结合临床病史、查体、影像学检查(尤其是MRI检查)及组织学检查,考虑有髓外复发可能。ALL生殖系统复发患者既往有ALL病史,其肿块通常呈双侧、无痛、弥漫性肿大,骨髓穿刺和脑脊液检查可见异型细胞支持ALL复发。而生殖系统原发肿瘤通常无血液病病史,其肿块通常呈单侧或双侧,可能有疼痛、局灶性结节,合并大量腹水或胸腔积液,肿瘤标志物如CA125、CA199、AFP等显著升高,经穿刺活检可见肿瘤细胞。正确鉴别生殖系统原发肿瘤与继发肿瘤,尽早获得有效治疗极为关键。由于生殖系统髓外复发临床罕见,对其治疗、预后的资料不足,无标准治疗方式,仍有待进一步积累资料,进行研究。

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