Egyptian Pediatric Association Gazette

CASE REPORT

Open Access

Precursor B-cell acute lymphoblastic leukemia presenting with isolated skin relapse: a pediatric case report

Yeter Düzenli Kar[1,2*], Zeynep Canan Özdemir[2], Ersin Töret[2], Evrim Yılmaz[3] and Özcan Bör[2]

Abstract

Background In childhood acute lymphocytic leukemia (ALL), relapse is most commonly seen in the bone marrow (10–20%), followed by the central nervous system (3–8%). Isolated skin relapse is very rare in ALL. We report an 8-year-old child presented with isolated skin relapse.

Case presentation An eight-year-old female patient presented with swelling on the scalp 3 months after the completion of the ALLIC-BFM 2009 chemotherapy protocol administered due to the diagnosis of precursor B-cell (pre-B) ALL. Physical examination revealed a hard, painless, hyperemic, nodule-shaped lesion measuring 2 × 1 cm on the right parietal bone. Atypical hematopoietic cells with the prominent nucleolus, narrow cytoplasm, and immunohistochemically stained with CD 10, 19, 22, 79-a, and TdT were observed in the histopathological examination of the skin lesion. There was no blast in the bone marrow aspiration smear and cerebrospinal fluid. The patient was diagnosed with aleukemic leukemia cutis (LC) and pre-B ALL, presenting as an isolated relapse.

Conclusion Aleukemic LC is a very rare finding after leukemia treatment. It may present with various cutaneous lesions, such as a papule, macule, plaque, nodule, palpable purpura, and ulcerative lesions. Leukemia cutis should be considered in the differential diagnosis of skin lesions developing during or after treatment in children with leukemia.

Keywords Aleukemic leukemia cutis, Child, Extramedullary relapse, Leukemia cutis, Pre-B ALL

Background

Acute leukemias account for up to 25–30% of childhood malignancies, making them the most common malignancies of childhood [1]. Acute lymphoblastic leukemia (ALL) constitutes 75% of acute leukemia in childhood [2]. Although the success of ALL treatment in children reaches 80–85% with the use of current advanced technology and chemotherapy protocols, relapse can still occur in 15–20% of the patients [3]. The most common sites of relapse are bone marrow (10–20%), followed by the central nervous system (CNS) (3–8%) and testicles (2%). Isolated skin relapse is very rare in ALL cases [1, 2]. The mechanism of skin relapse is not yet fully known [4]. We report an 8-year-old child presented with isolated skin relapse when the patient was in bone marrow remission 3 months after the completion of ALL treatment.

Case presentation

An 8-year-old female patient presented with swelling on the scalp 3 months after the completion of the ALLIC-BFM-2009 chemotherapy protocol administered due to the diagnosis of precursor B-cell (pre-B) ALL. No blast was observed in the bone marrow aspiration and cerebrospinal fluid (CSF) examination performed during

*Correspondence:
Yeter Düzenli Kar
yeterduzenli@yahoo.com
[1] Division of Pediatric Hematology/Oncology, Department of Pediatrics, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey
[2] Division of Pediatric Hematology/Oncology, Department of Pediatrics, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey
[3] Department of Pathology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Turkey

treatment discontinuation and in the posttreatment 6th week. Her physical examination revealed a hard, painless, hyperemic, nodule-shaped lesion measuring 2 × 1 cm on the right parietal bone (Fig. 1). There was no pathological lymphadenopathy or organomegaly in the systemic examination. Laboratory test results were as follows: hemoglobin (Hb) was 13.4 g/dL, white blood cell (WBC) was 6500/mm^3, absolute neutrophil count (ANC) was 3100/mm^3, and platelet (PLT) count was 178,000/mm^3. C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and uric acid levels were 0.3 mg/dL (0–0.8), 28 IU/L (0–41), 33 IU/L (0–37), 270 IU/L (120–300), and 3.9 mg/dL (2.2–6.4), respectively. There were no blasts in the peripheral blood smear. Amoxicillin-clavulanic acid was initiated with the preliminary diagnosis of soft tissue infection to treat the lesion. Upon the absence of regression in lesion size with antibiotherapy during a 14-day was follow-up, an excisional biopsy was performed on the lesion. Atypical hematopoietic cells with a prominent nucleolus, narrow eosinophilic cytoplasm (Fig. 2), and immunohistochemically stained with CD-10, CD-19, CD-22, CD-79a, and TdT were observed in the histopathological examination of the skin lesion and reported to be compatible with leukemia cutis (LC). There was no blast in the bone marrow aspiration smear and CSF. The patient was diagnosed with aleukemic LC (ALC). CD-10, CD-19, CD-22, CD-79a, and TdT evaluated at the time of the initial ALL diagnosis were positive in the flow cytometry. Furthermore, the t(9; 22), t(4; 11), t(1; 19), and t(12, 21) tests examined at the time of the initial diagnosis were negative. No pathology was detected in cranial magnetic resonance imaging (MRI). The patient was considered to be in the intermediate-risk group (S2) according to the ALL-REZ-BFM-02 protocol, and systemic chemotherapy was initiated. The ALL-REZ-BFM-02 protocol was completed 10 months ago reporting of case, and outpatient follow-up continues with remission.

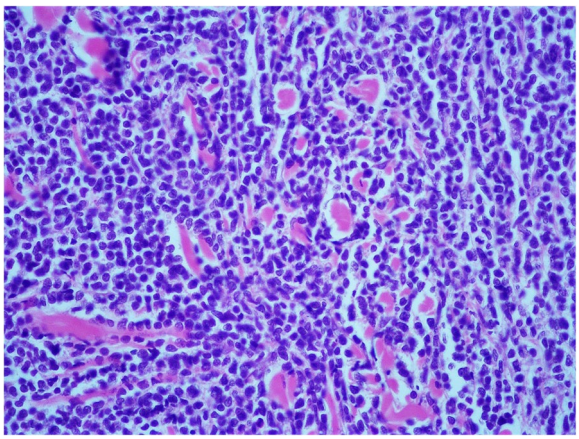

Fig. 2 Skin tissue with leukemic infiltration

Written informed consent was obtained from the patient's family.

Discussion

LC is caused by the invasion of neoplastic cells into the epidermis, dermis, or subcutis. It may present with various cutaneous lesions, such as papule, macule, plaque, nodule, palpable purpura, and ulcerative lesions [5, 6]. Whereas there are studies reporting its presence at the upper extremities, back, trunk, face, and scalp, it is most commonly reported in the lower extremities. Its incidence is 10–15% in acute myeloid leukemia (AML) and 1–3% in ALL [7]. LC is mainly seen in the myelomonocytic, and monocytic subtypes of AML, and is defined as myeloid and granulocytic sarcoma [8]. It is reported to be rarer in pre-B ALL cases [7]. Although LC often presents with the initial diagnosis of leukemia, it may rarely occur after the initial diagnosis or during relapse. If it occurs as isolated extramedullary involvement without blood or bone marrow involvement, it is called ALC. Leukemic relapse presenting as isolated ALC is an unusual clinical observation in childhood leukemia [1, 5]. In the literature, four pediatric cases of relapsed ALL are presented as ALC. One of these cases was T-ALL-associated LC, whereas two were pre-B-ALL-associated LC and one was

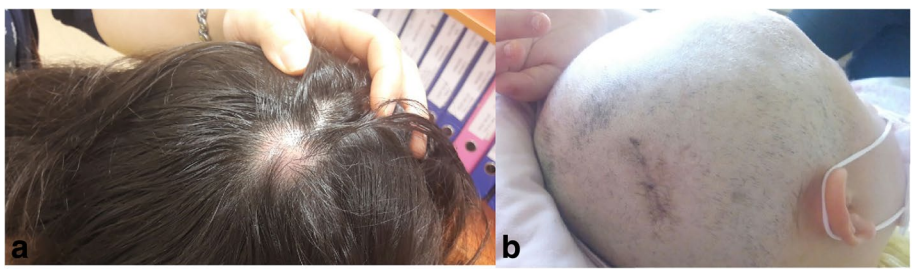

Fig. 1 Preoperative and postoperative leukemia cutis lesion image

Table 1 Pediatric cases diagnosed with relapse presenting as aleukemic leukemia cutis

No of patients	Reference	Age	Leukemia type	Characteristics of children diagnosed with ALC
1	Joshi K, et al. [6]	2	Pre-B-ALL	The patient was diagnosed with pre-B ALL (isolated bone marrow involvement) at the age of two. ALC was identified on the 28th day of the BFM protocol while the bone marrow was in remission. The patient developing bone marrow and testicular relapse died in the second month of the BFM relapse protocol.
2	Shahriari et al. [1]	8	T-cell ALL	The patient was diagnosed with T-ALL (isolated bone marrow involvement) at the age of eight. ALC relapse (hard palate, lips, and skin) was identified two years following the completion of the treatment. Prognosis: lesions regressed in the second week after chemotherapy and the patient became a transplant candidate.
3	Mohammadi Ashiani et al. [9]	9	Pre-B-ALL	The patient was diagnosed with pre-B ALL (bone marrow involvement and ulcerated lesions on the skin) at the age of five and with testicular and bone marrow relapse at the age of nine. During the ALL-REZ BFM protocol, isolated LC was identified on the face following the R1-R2 block. No information about the prognosis was provided.
4	Pavon-Mengual M, et al. [10]	10	common B lineage ALL	At the age of 10, isolated skin relapse was identified 22 months after the B-ALL treatment was completed. Prognosis: lesions regressed in the second week after chemotherapy. No information about the prognosis was provided.

ALL Acute lymphocytic leukemia, *ALC* Aleukemic leukemia cutis

common B-ALL-associated LC (Table 1) [1, 5, 9, 10]. To our knowledge, this is the fourth case report presenting a child with relapsed B-ALL-associated ALC.

In a study conducted by the ALL-REZ Study Group, it was reported that they found relapse in 132 (5.7%) of 2323 ALL children, 54 isolated extramedullary relapse, and 10 isolated skin relapses. It has been reported that isolated extramedullary relapses are rare and have a poor prognosis [11].

The pathogenesis of LC has not been fully elucidated yet [5]. Leukemia cutis is accepted as a marker of disease resistance. The occurrence of LC following the diagnosis of leukemia indicates that (i) hematological relapse or extramedullary relapse may occur in a short time, or (ii) resistance to chemotherapy can be seen [1, 12]. In the present case, no bone marrow or extramedullary relapse was identified for about 3 years after the relapse protocol was initiated. One of four cases reported in the literature was a 2-year-old patient with pre-B ALL. The case was reported to die due to bone marrow and testicular relapse 2 months after the development of isolated skin relapse [2]. However, the other three cases provided no information about the long-term prognosis [5, 9, 10].

There is no specific treatment for LC; skin lesions regress spontaneously with the leukemia treatment. The primary purpose of treatment is to eliminate systemic disease by chemotherapy or hematopoietic stem-cell transplantation [13]. Although achieving and maintaining bone marrow remission with systemic chemotherapy are sufficient for most patients with LC, it cannot control skin involvement in some patients. Therefore, treatment options focusing directly on the skin, such as radiotherapy, are recommended for cases without improvement after systemic chemotherapy [12].

There was no need for adjuvant therapy other than systemic chemotherapy since our patient had a single, nodule-shaped lesion on the skin; this lesion was removed entirely through excisional biopsy, and no new skin lesions developed under systemic chemotherapy.

Conclusion

İsolated skin relapse is a very rare condition in ALL patients. Leukemia cutis may present with various cutaneous lesions, such as papule, macule, plaque, nodule, palpable purpura, and ulcerative lesions [5]. Therefore, ALC skin lesions may be confused with allergic, infectious, and vasculitis-like diseases. In cases presenting with infectious, allergic, and vasculitis-like findings, a biopsy and histopathological examination should be performed in the presence of a skin lesion resistant to the treatment. During the follow-up of patients receiving treatment for leukemia, skin relapse, as well as bone marrow, CNS, and testicular relapse, should be kept in mind, and isolated skin relapse should be considered in the differential diagnosis of skin lesions in these patients.

Abbreviations

ALT	Alanine aminotransferase
ALL	Acute lymphoblastic leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
CNS	Central nervous system
CSF	Cerebrospinal fluid
CRP	C-reactive protein
Hb	Hemoglobin

LDH	Lactate dehydrogenase
PLT	Platelet
pre-B cell	Precursor B cell
WBC	White blood cell

Acknowledgements
None.

Authors' contributions
YDK, ÖB, ZCÖ, EY, and ET contributed to the conception and design of the work. Analysis and interpretation of data were performed by all authors. All authors were involved in drafting of the work, and it was revised by all authors. The authors read and approved the final manuscript.

Funding
There is no funding.

Availability of data and materials
None.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report.

Competing interests
The authors declare that they have no competing interests.

Received: 19 January 2023 Accepted: 10 March 2023
Published online: 10 May 2023

References

1. Shahriari M, Fathpour G, Saleh F (2016) Mucocutaneous relapse as an unusual presentation of T-lineage acute lymphoblastic leukemia. Middle East J Cancer 7(1):63–66
2. Carrol WL, Bhatla T. (2016) Acute lymphoblastic leukemia. In: Lanzkowsky P, Lipton JM, Fish JD (eds). Lanzkowsky's Manual of Pediatric Hematology and Oncology (6th ed). New York: Academic Press, 367-387. https://doi.org/10.1016/B978-0-12-801368-7.00015-6.
3. Locatelli F, Schrappe M, Bernardo ME, Rutella S (2012) How I treat relapsed childhood acute lymphoblastic leukemia. Blood 120(14):2807–16. https://doi.org/10.1182/blood-2012-02-265884
4. Le Lee E, Park HJ, Cho BK, Lee JY, Lee S (2010) Leukemia cutis as early relapse of T-cell acute lymphoblastic leukemia. Int J Dermatol 49(3):335–7. https://doi.org/10.1111/j.1365-4632.2009.04255.x
5. Wagner G, Fenchel K, Back W, Schulz A, Sachse MM (2012) Leukemia cutis - epidemiology, clinical presentation, and differential diagnoses. J Dtsch Dermatol Ges 10(1):27–36. https://doi.org/10.1111/j.1610-0387.2011.07842.x
6. Joshi K, Panchal H, Parikh S, Modi G, Talele A, Anand A, Uparkar U, Joshi N, Khatawani I (2016) Aleukemic leukemia cutis presenting as a sole sign of relapsed paediatric acute lymphoblastic leukemia. Indian J Hematol Blood Transfus 32:46–9. https://doi.org/10.1007/s12288-015-0597-z
7. Campuzano-García AE, Torres-Álvarez B, Castanedo-Cázares JP (2015) Leukemia cutis in a patient with pre-B-cell acute lymphoblastic leukemia. JAAD Case Rep 1(6):364–7. https://doi.org/10.1016/j.jdcr.2015.08.005
8. di Meo N, Pozzato G, Leonardo E, Trevisini S, Vichi S, Trevisan G (2017) A transient cutaneous relapse of AML M1 in hematological remission: a case report. Acta Dermatovenerol Alp Pannonica Adriat 26(4):109–111. https://doi.org/10.15570/actaapa.2017.31
9. Mohammadi Ashiani A, Madani F (2016) Leukemia cutis in a child with acute lymphoblastic leukemia at diagnosis and relapse. IJBC 8(2):61–62
10. Pavon-Mengual M, Horgan C, Motwani J, Velangi M (2019) Combined skin lesions of leukaemia cutis and septic emboli in a child with relapsed acute lymphoblastic leukaemia. Br J Haematol 185:186–186 (111 River St, Hoboken 07030-5774, Nj Usa: Wiley)
11. Lissat A, van Schewick C, Steffen IG, Arakawa A, Bourquin JP, Burkhardt B, Henze G, Mann G, Peters C, Sramkova L, Eckert C, von Stackelberg A, Chen-Santel C (2021) Other (non-CNS/testicular) Extramedullary localizations of childhood relapsed acute lymphoblastic leukemia and lymphoblastic lymphoma-a report from the ALL-REZ Study Group. J Clin Med 10(22):5292. https://doi.org/10.3390/jcm10225292
12. Karapinar DY, Kamer SA, Karadaş N, Anacak Y, Delcastello BE, Balkan C, Kavakli K, Aydinok Y (2015) Successful treatment with total skin electron beam therapy in a child with isolated cutaneous relapsed AML. J Pediatr Hematol Oncol 37(6):e372-4. https://doi.org/10.1097/MPH.0000000000000342
13. Özkur E, Aksu AE, Falay T, Gürel MS, Leblebici C (2018) Hemorajik Ülserasyon ve Sweet Benzeri Lezyonlarla Seyreden Lösemi Kutis: Olgu Sunumu. Turk J Dermatol 12:154–6. https://doi.org/10.4274/tdd.2391

Publisher's Note