OPIS PRZYPADKU CASE REPORT

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Aleukemic leukemia cutis as a manifestation of acute lymphoblastic leukemia in a 13-year-old girl

Aleukemiczna białaczka skóry jako manifestacja ostrej białaczki limfoblastycznej u 13-letniej dziewczynki

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Key words

aleukemic leukemia, atypical cells, child, leukemia cutis, skin infiltration, skin lesions

Słowa kluczowe

aleukemiczna białaczka, komórki atypowe, dziecko, białaczka skóry, nacieczenie skóry, zmiany skórne

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Summary

Cutaneous manifestations of leukemia may present two forms: specific malignant lesions – leukemia cutis (LC) and non-specific "leukemids", where leukemia is accompanied by benign cutaneous lesions – vasculitis, erythrodermy, erythema nodosum or Sweet's syndrome. Leukemia cutis is caused by infiltration of blast cells into the skin.

Leukemia cutis (LC) is observed mostly in patients with myeloid leukemia, especially the myelomonocytic and monocytic types of AML in adolescents and adults. In children similar lesions are very uncommon. They occur in approximately 25-30% of congenital leukemias and are often accompanied by congenital defects, organomegaly and karyotype abnormalities. However, LC is unusual in ALL and the frequency may be as low as 1%. In older children, the incidence of leukemia cutis at diagnosis is 10% in AML while very little is known about the malignant cutaneous involvement in acute lymphoblatic leukemia (ALL).

Streszczenie

W przebiegu białaczki mogą wystąpić dwa rodzaje zmian skórnych. Jedne z nich są niespecyficzne, przybierają postać tzw. „leukemidu" – zapalenie naczyń, rumień, rogowaciejąca eytrodermia, rumień guzowaty albo zespół Sweeta. Specyficzne zmiany – tzw. białaczka skóry, są związane z naciekaniem przez komórki nowotworowe.

Postać skórna białaczki częściej obserwowana jest u pacjentów z rozpoznaniem białaczki szpikowej, szczególnie mielomonocytowej i monocytowej – u chorych dorosłych i młodzieży. U dzieci podobne zmiany są rzadkością. Zdarzają się u 25-30% dzieci w przebiegu białaczki wrodzonej, często towarzyszą im inne zaburzenia: wady rozwojowe, organomegalia, zaburzenia genetyczne. W białaczce limfoblastycznej zmiany na skórze są bardzo nietypowe, zdarzają się rzadziej niż w 1% przypadków. U dzieci starszych, przypadki białaczki skóry rozpoznawane są u blisko 10% dzieci z ostrą białaczką szpikową (ang. *acute myeloid lekemia* – AML) i u mniej niż 1% pacjentów z ostrą białaczką limfoblastyczną (ang. *acute lymphoblastic leukemia* – ALL).

We describe a case of 13-year-old girl, who was presented with a localized subcutaneous tumor on the right arm. Skin over the lesion showed purpura, but wasn't pruritic, painful, or tender. Patient was otherwise in good health and had no other symptoms. Biopsy of the lesion revealed a dense, monomorphous infiltration of the skin formed by T-lymphoid cells. Hematological findings specific for leukemia – decrease of hemoglobin level, platelet count and eventually occurrence of blasts in the peripheral blood – appeared nearly a year from later. A bone marrow biopsy confirmed the diagnosis of acute lymphoblastic bilinear leukemia.

CASE PRESENTATION

13-year-old, otherwise healthy girl was admitted to the Rheumatology Department for diagnosis of a nodular skin lesion of the right arm, observed for previous 4 months. On admission patient was in a good general condition, affebrile, and wasn't complaining of any pain in the affected arm. Physical examination revealed a round tumor in the subcutaneous tissue just below the skin, 5 cm in diameter, with accompanying cyanosis and peripheral erythema on the surface. No other signs or symptoms were noted.

Ultrasound scan of the soft tissue showed thickening and oedema of dermis. Between the skin and the subcutaneous tissue there was a irregular, vascularised, hypoechogenic tumor 45 mm in diameter. Right next to it there was a similar, smaller change 4 mm in diameter.

Laboratory test results were all within normal range.

Connective tissue disorders were excluded. For the next 6 months a girl was developing normally with no systemic symptoms, but the size of the lesion was increasing, erythema and skin warming become more pronounced (fig. 1).

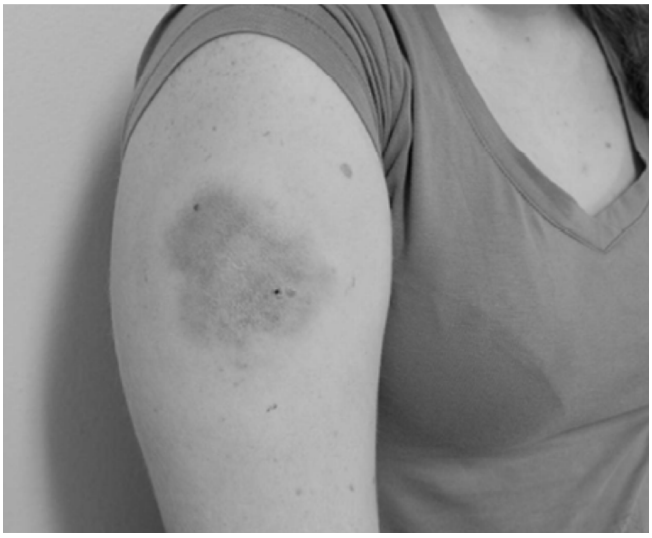

Fig. 1. Skin lesion after 10 months from presentation.

After nearly a year from presentation girl started to complain joint pain affecting knees, elbows and wrists with accompanying oedema and reduction in the range of movement. She became prone to airway and gastrointestinal infections. A biopsy of the lesion was finally performed (fig. 2 and 3).

Evaluated fragment of the skin contained profuse infiltration composed mostly of T lymphocytes (CD 3+, CD 13+) with single lymphocytes B (CD 20+), multiple macrophages (CD 68+) and a few S-100+ cells. Proliferative activity of the observed lymphocytic population showed minor expression Ki67 (circa 50%).The presence of antigens Tdt, CD 7, CD1a, CD 34, CALLA, CD79a and MPO was not identified. Epidermotropic properties of the infiltration were noted.

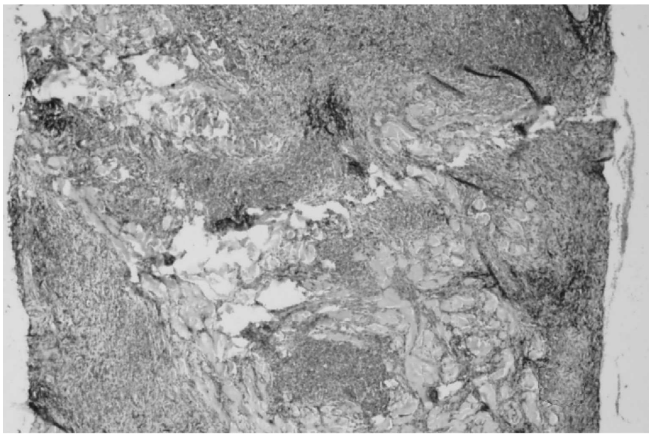

Fig. 2. Hematoxylin-eosin staining (× 20) showing a diffuse cellular infiltration involving the subcutis, arising between collagen bundles.

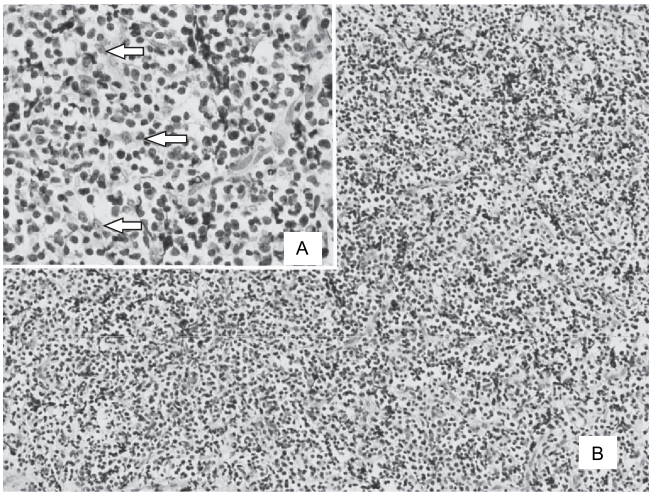

Fig. 3. (A) Skin biopsy x 100, (B) atypical cellular infiltrate consisting of mononuclear cells in the dermis x 400 (arrows) cells have abundant cytoplasm and irregular nuclei with some prominent nucleoli (inset; haematoxylin and eosin stain).

Laboratory results at the admission were within the normal ranges, however patient's general status was worsening. Revised tests revealed a number of abnormalities (tab. 1).

Table 1. Evolution of laboratory results.

Parameter	Laboratory results at the beginning of hos	Laboratory results during hospitalisation
Hb	13.6 g/dl	9.4 g/dl
PLT	264*10 ^ 3/ul	126*10 ^ 3/ul
WBC	13.54*10 ^ 3/ul	8.72*10 ^ 3/ ul
Smear Results		
Neutrophiles	63%	6%
Bands	1%	1%
Limphocytes	30%	26%
Monocytes	6%	2%
Atyoical cells	0%	65%
Inflammatory Markers Results		
CRP	2.3 mg/dl	14 mg/dl
ESR	11 mm/h	73 mm/h
Ferritin	168 ng/ml	555 ng/ml
Uric Acid	5.7 mg/dl	11.2 mg /dl
LDH	253 u/l	2121 u/l

Bone marrow biopsy showed a monotone image with very high amount of cells in the bone marrow matrix with 93% of blastic, medium sized cells. Aplasia of other hematopoetic cell lines was noted. In cytochemical tests, PAS reaction was positive in 7% of blasts, POX reaction was negative. Based on the tumor cell immunophenotype – expression of markers: TdT+, CD7+, CD10+, CD13, CD19+, CD20+, CD22+, CD34+, CD45+, CD79a+, patient was diagnosed with acute lymphoblastic bilinear lekemia ALL – pre-B common (+) with co-expression of CD7+ and CD13+ (tab. 2).

Table 2. Tumor cell immunophenotype in bone marrow.

Fenotype of hematopoetic cells	Percentage of expression (%)
CD 3	1
CD 5	6
CD 7	81
CD 19	92
CD 10	81
CD 20	90
CD 22	47
CD 79a	92
CD 22 cytoplasmatic	26
MPO	12
CD 13	86
CD 14	4
CD15	8
CD33	8
CD 117	3
CD 34	70
HLA DR	35
TdT	36
CD 45	30

Final diagnose ALL – pre-B common (+) with CD 7 and CD 13 co-expression

Prior the final diagnose patient administered NSAIDs orally, used also topical steroids. Administration was not regular.

Cytogenetic studies ruled out the presence of unfavourable prognostic fusion genes: BCR/ABL and MLL/AF4. Patient was stratified to the intermediate risk group IR and started therapy according to ALLIC 2002 protocol. The patient underwent remission induction chemotherapy consisting ALLIC 2002 standard doses of therapeutics. Complete hematological remission was obtained on 15th day during inducting chemotherapy and the skin lesion, as well as the mass on the right arm region, disappeared after the first month of treatment. A girl successfully completed a maintenance therapy in December 2011 and remains in remission for the last 7 months.

DISCUSSION

Clinical appearance of leukemia cutis is variable, typically manifests as red or violaceous, localized or disseminated papules, multiple 1 to 2.5 cm nodules, or plaques, ranging from a solitary lesion to involvement of 70% of the body surface area, affects face mainly (1).

Histopatologic examination of lesions usually shows a dense, diffuse, monomorphus infiltrate. Leukemic cells are predominantly small to medium sized lymphoid cells with a high nucleus to cytoplasmic ratio or clefted nucleus. Infiltration is diffuse in distribution and usually involve all layers of the dermis and subcutis (2, 3).

Skin infiltration may be confused with other non-specific skin lesions and becomes a serious clinical problem. Many reports shows that LC may mimic a purpuric, haemorrhagic, inflammatory or infective lesions. It is therefore tough to know the authentic incidence of hematopoetic neoplasia with cutaneous manifestation (4, 5). Similar skin changes were reported in our case (tab. 3).

Table 3. Forms of leukemia cutis (LC) (4, 5).

Infiltration forms simulated by leucemia cutis
Vasculitis
Exfoliative erythroderma
Bullous pyoderma gangrenosum
Erythema multiforme
Urticaria
Respond to antimicrobial and/or blood product support

Leukemia cutis as an initial manifestation is relatively unusual with a reported incidence of 3.1% of all LC cases. Occurrence of leukemic cells infiltration of the skin is present before the typical abnormalities in the peripheral blood and bone marrow, it is referred to as “aleukemic leukemia cutis” (ALC) (6, 7) and it is frequently misdiagnosed and treated as lymphoma or primary skin disease (8, 9).

It proves that even benign looking skin changes in children require vigilant observation and sometimes extensive diagnostics. The value of histopathological and immunohistochemical examination can’t be overestimated, specially in cases with no other clinical symptoms.

There are only a few published pediatric cases of patients with ALL, in whom cutaneous infiltration was an early manifestation of malignancy (ALC). In 90’s, an article was published by collaborators from EORTC, who reviewed the records of almost 1300 patients with ALL. Skin involvement was the initial sign of the hemopathy, and a lesions preceded the diagnosis in three patients (10). Najem et al. (11) published a case report of a boy with 6-month history of intermittent erythema nodosum-like lesions on both shins, in whom a biopsy from one of the cutaneous nodules showed diffuse lymphoid cell infiltrate. Patient was diagnosed with T-cell ALL. Ali et al. (9) published a case of misdiagnosed as a lymphoma 16-year-old girl (tab. 4).

Medline research reveal that our case is one of the six cases of aleukemic leukemia cutis (ALC) observed in children with ALL and reported in the English-language literature (9-11).

Table 4. Aleukemic leukemia cutis (ALC) in pediatric patients with ALL cases – Pubmed rewiev.

Author	Sex/Age	Diagnosis	Dermatological findings	Cytological findings	Immunohistochemical findings
Millot et al. (10)	9 month 5 y.o. 8 y.o.	ALL	Changes localized mainly on face	No data	No data
Najem et al. (11)	M/8 y.o.	T-cell ALL	Erythema nodosum-like lesions on both shins	The lymphoid cells characterized as lymphoblasts with large vesicular nuclei containing nucleoli	Blast cells positive for CD3, CD45 CD45RO negative for CD20 and CD68
Ali et al. (9)	F/16 y.o.	Primary misdiagnosed as lymphoma T-cell ALL	Maculopapular lesions 1-2 cm in diameter widespread all over the body and a mass of 10 cm in diameter on the right anterior femoral region	Skin involvement in the dermis by small round cells with large nuclei	Blast cells positive for CD45R0, CD3 negative for CD34, CD20, CD79A
Presented case	F/13 y.o.	Bilinear ALL – leukemia pre-B common (+) with co-expression of CD7+ and CD13+	Round tumor in the subcutaneous tissue just below the skin, 5 cm in diameter, with accompanying cyanosis and peripheral erythema on the surface	Atypical cellular infiltrate consisting of mononuclear cells in the dermis cells with abundant cytoplasm and irregular nuclei with some prominent nucleoli	Blast cells positive for TdT, CD7, CD10, CD13, CD19 CD20, CD22, CD34, CD45, CD79a

CONCLUSIONS

Presented case is unique for several reasons. Firstly it is extremely rare situation when skin changes are the primary manifestation of ALL. Moreover it is not typical that ALL has developed during long, almost 1 year, asymptomatic period. Generally ALL progresses suddenly and turbulently. It takes only few weeks to develop fully symptomatic disease. Our case indicates that diagnostic process of ALL should also include dermatological consideration related to leukemia cutis.

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