

A newborn with congenital mixed phenotype acute leukemia with complex translocation $t(10;11)(p12;q23)$ with *KMT2A/MLLT10* rearranged – a report of an extremely rare case

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Abstract

Neonatal congenital leukemia (CL) constitutes less than 1% of all childhood leukemia cases and is diagnosed in 1 to 5 per million live births. In the neonatal period acute myeloid leukemia (AML) is described in 56-64% of cases, acute lymphoblastic leukemia (ALL) in 21-38% of cases and mixed-phenotype acute leukemia (MPAL) in less than 5% of cases. Rearrangements of the mixed-lineage leukemia (*KMT2A* alias *MLL*) gene are found in > 70% of infant leukemia cases. The incidence of the most frequent *KMT2A* rearrangements in newborns with congenital MPAL is unknown. We report a male term newborn with “blueberry muffin” syndrome, which had been noted at birth, as a presenting sign of acute leukemia. Eight-color multiparameter flow cytometry showed a blast population corresponding to a myeloid lineage with monocytic differentiation positive for *CD33+*/*CD15+*/*CD11c+*/*CD64+*/*HLA-DR+*/*CD4+*, negative for *MPO*-/*CD34*-/*CD19*-/*CD79a*-/*CD117*-/*CD13*-/*CD14*-/*CD36*-/*CD3*-/*CD2*-/*CD7*-, and additionally positive for *sCD3* (40%). Mixed-phenotype acute leukemia according to the World Health Organization (WHO) classification was diagnosed with complex translocation $t(10;11)(p12;q23)$ with *KMT2A/MLLT10* rearrangement. The patient had an unfavorable response to chemotherapy and died on the 5th day of life.

Key words: newborn, congenital leukemia, mixed phenotype acute leukemia.

(*Centr Eur J Immunol* 2018; 43 (3): 346-352)

Introduction

Neonatal congenital leukemia (CL) constitutes less than 1% of all childhood leukemia cases and is diagnosed in 1 to 5 per million live births. In the neonatal period (up to 28 days after birth) acute myeloid leukemia (AML) is described in 56-64% of cases, acute lymphoblastic leukemia (ALL) in 21-38% of cases and mixed-phenotype acute leukemia (MPAL) in less than 5% of cases [1]. Several factors may be associated with the development of leukemia in a newborn: maternal exposure to radiation, high birth weight, high level of insulin-like growth factors, exposure to marijuana, and topoisomerase-II inhibitors such as coffee, tea,

cocoa, wine, and soy products [2, 3]. Diagnosis of perinatal leukemia should be based on three major criteria: presence of immature hematopoietic cells in the peripheral blood and bone marrow, hematopoietic cell infiltration into non-hematopoietic tissue, and exclusion of other conditions by differential diagnosis [1]. In 25-30% of all cases infiltration of subcutaneous tissues by leukemic cells is found. Skin symptoms are called “blueberry-muffin” syndrome and should be differentiated from TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus), blue rubber bleb nevus syndrome, Langerhans cell histiocytosis, cutaneous mastocytosis and other hematological disorders [3]. The prog-

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Submitted: 3.07.2018; Accepted: 21.08.2018

nosis of CL remains poor, although spontaneous remissions are observed [4].

Rearrangements of the mixed-lineage leukemia (*KMT2A* alias *MLL*) gene are found in > 70% of infant leukemia cases and generally confer a poor prognosis. There are more than 120 known fusion partners of *KMT2A* having some correlation with disease phenotype and prognosis. *AF4/KMT2A* fusion, a result of a $t(4,11)(q21,q23)$ translocation, is responsible for approximately 50% of cases of infant acute leukemias. *ALL1*-fused from chromosome 9 (*AF9*) and eleven-nineteen leukemia (*ENL*) are the second and third most common fusion partners of *KMT2A*, and these fusions arise from the $t(9,11)(p22,q23)$ and $t(11,19)(q23,p13.3)$ translocations [5]. The incidence of the most frequent *KMT2A* rearrangements in newborns with congenital MPAL is unknown. The first neonatal case report of congenital MPAL in the literature was described in 2015. However, in this case cytogenetic analysis showed a normal female karyotype, and FISH results for translocations or deletions involving the *KMT2A* gene and for monosomy 7 or 7q deletions were negative [6].

Case report

Clinical course

We report a case of a male infant born in the Clinical Hospital of Gynecology and Obstetrics at the Poznan Uni-

versity of Medical Sciences at 40 weeks of gestation to a 38-year-old gravida 1 mother, whose pregnancy had been uncomplicated. The detailed history for maternal exposure to mutagenic agents or an underlying genetic predisposition for malignancy was negative. The infant was delivered via caesarean section for fetal decelerations following the spontaneous onset of labor. Apgar scores were 4 and 8 at 1 and 5 minutes of life, respectively. After the birth in the 3rd minute of life the neonate was intubated due to respiratory insufficiency and was admitted to the Neonatal Intensive Care Unit, Department of Neonatology, Poznan University of Medical Sciences. Initial examination of the skin confirmed diffuse, multiple dome-shaped, bluish-red violaceous, non-tender papules and nodules (blueberry muffin appearance) and multiple petechiae (Fig. 1). There was decreased spontaneous movement associated with decreased muscle tone of upper and lower extremities.

On the 2nd day of life the patient was extubated, and on non-invasive ventilation support transported to the Department of Pediatric Oncology, Hematology and Transplantation (DPOHT), Poznan University of Medical Science. On admission, the clinical condition of the neonate was severe, with respiratory distress, poor activity, multiple skin hemorrhages, and generalized neonatal scleroderma. Laboratory findings indicated hypoxemia, lactic acidosis and coagulopathy. Cranial ultrasound showed increased periventricular echogenicity. In abdominal

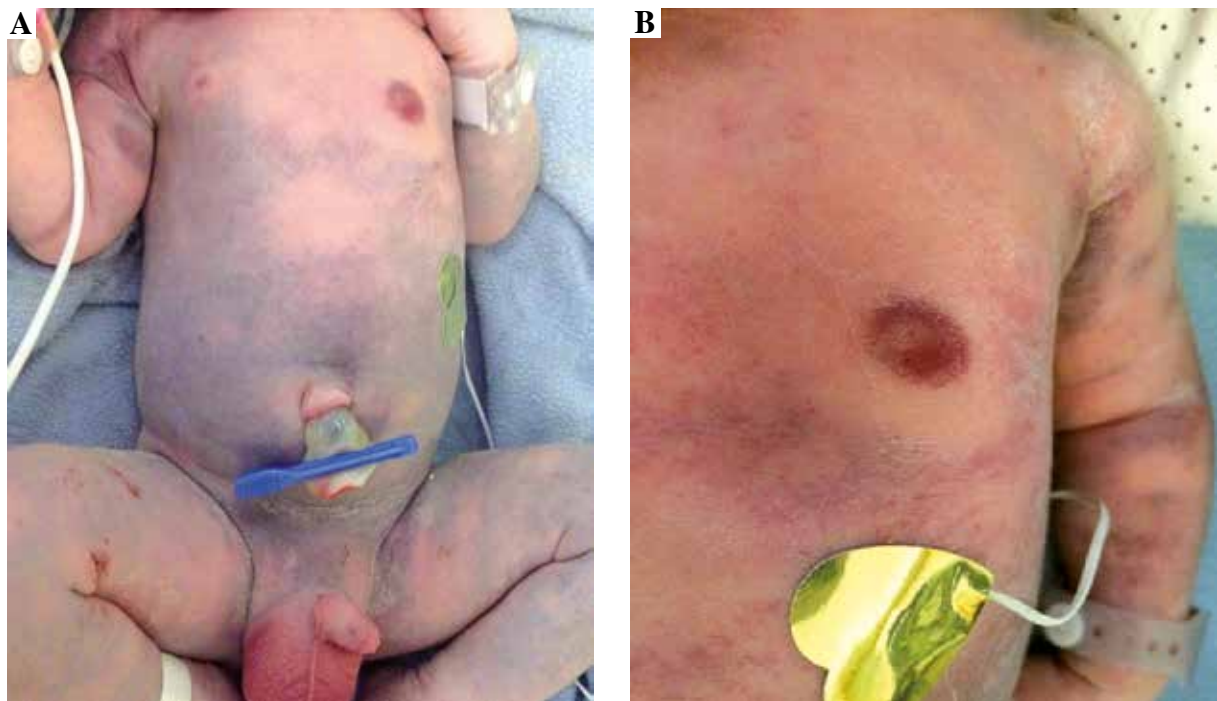


Fig. 1. Multiple dome-shaped, bluish-red violaceous, non-tender papules and nodules (blueberry muffin appearance) and multiple petechiae

ultrasound hepatosplenomegaly was found. Pleural and testicular ultrasound results were normal.

Laboratory, flow cytometry and genetic findings

Initial laboratory studies done in the first hours of life showed hyperleucocytosis (91.6 G/l, normal range: 8-30 G/l), anemia (hemoglobin level – 7.1 mmol/l, normal range: 8.3-12.4 mmol/l; hematocrit – 0.317 l/l, normal range 0.396-0.573 l/l) and thrombocytopenia (20 G/l, normal range: 114-449 G/l). Laboratory findings specific for tumor lysis syndrome, including elevated uric acid level (9.3 mg/dl, normal range: 3-5 mg/dl), were found.

Bone marrow aspiration performed on the 1st day of life showed infiltration by leukemic cells (48%), predominantly promonocytes. Eight-color multiparameter flow cytometry showed a blast population corresponding to a myeloid lineage with monocytic differentiation positive for CD33+/CD15+/CD11c+/CD64+/HLA-DR+/CD4+, negative for MPO-/CD34-/CD19-/CD79a-/CD117-/CD13-/CD14-/CD36-/cCD3-/CD2-/CD7-, and additionally positive for

sCD3 (40%). Mixed-phenotype acute leukemia (MPAL) according to the WHO classification was diagnosed [7].

Chromosomal analysis of a peripheral blood sample was performed on 23 metaphases, two of which showed a normal karyotype. Translocation involving the p and q arm of chromosome 10 and the q arm of chromosome 11 was detected in 21 metaphases (86%). The translocation was found as the sole abnormality in 6 metaphases and with additional monosomies in the remaining 10 hypodiploid and 5 hyperhaploid ones. Interphase FISH study confirmed 11q23 rearrangement (*KMT2A* gene locus) in 80% of interphase nuclei examined. Metaphase FISH with a *KMT2A* probe showed a 3' *KMT2A* signal (red) on the short arm of derivative chromosome 10 (der(10)) and 5' *KMT2A* on derivative 11 (Fig. 2C), a WCP10 probe was present on der(10) and on derivative 11 (der(11)) (Fig. 2D), and additionally a 10qtel probe (D10S2290) was present on the q arm of the normal chromosome 10 and the long arm of der(10) (Fig. 2). The karyotype was defined as:

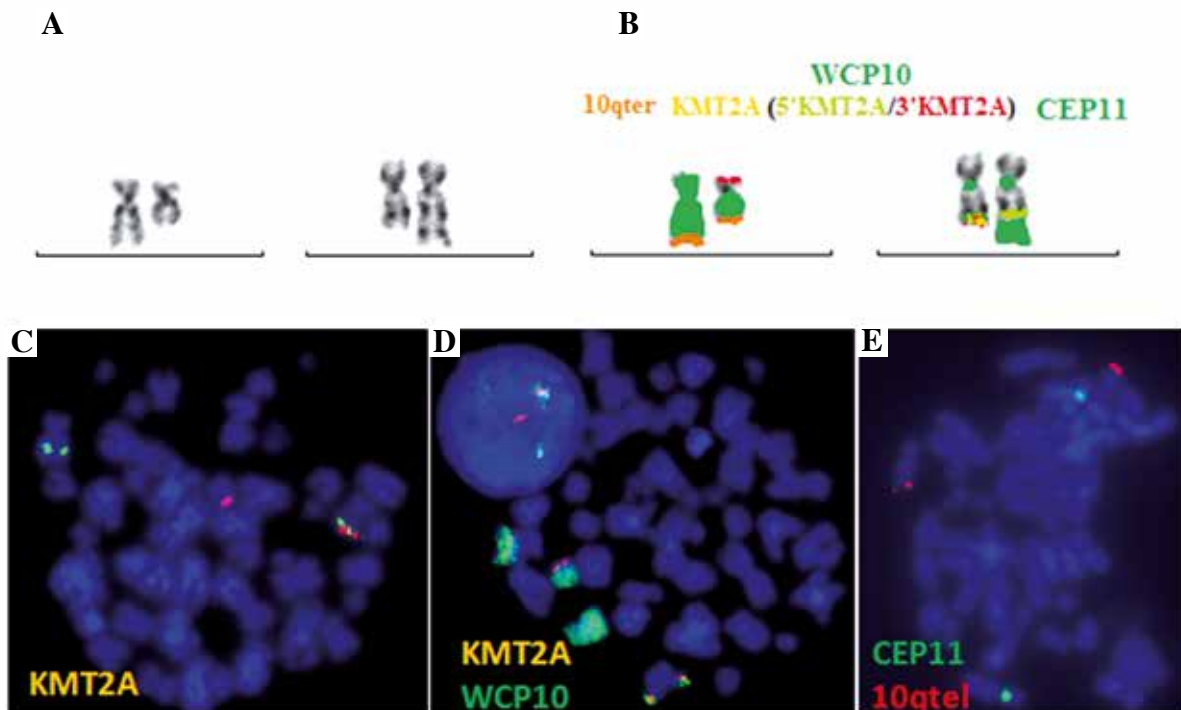


Fig. 2. A) G-banding patterns of chromosomes 10 and 11; B) G-banding patterns of chromosomes 10 and 11 with graphic interpretation of rearrangements involving 10p, 10q and 11q; C) Fluorescence *in situ* hybridization (FISH) using MLL break-apart probe on a metaphase showed a *KMT2A* rearrangement – split signal (red and green) and the normal colocalized red-green signal; D) FISH using MLL break-apart probe and whole chromosome painting probe for chromosome 10 (WCP10) reveals translocation of 10q to 11q; E) FISH using 10q telomere probe (D10S2290) and 11 centromere probe (CEP11) reveals 10qtel probe signals on normal 10 and der(10) chromosomes

46,XY,der(10)(?:p12→q?:q?),der(11)(11pter→11q23::10q?24→10q?)[6]/43~45,XY,-1[2],-6[2],der(10)(?:p12→q?:q?)[10],der(11)(11pter→11q23::10q?24→10q?)[10],-16[2],-19[3],-21[5][cp10]/32~34,X,-Y[2],-1[2],-2[2],-3[2],-5[3],-6[2],-7[3],der(10)(?:p12→q?11.2::?) [4],der(11)(11pter→11q23::10q?24→10q?)[4],-11[4],-15[5],-16[2],-17[4],-18[4],-18[3],-19[4],-20[3],-21[5],-22[5][cp5];

ish der(10)(?:10p12→10q?)(3'MLL+,wcp10+,D10S2290+),der(11)(11pter→11q23::10q?24→10q?)(D11Z1+,5'MLL-,3'MLL-,wcp10+)/46,XY[2].

To confirm the cytogenetic findings and identify the *KMT2A* gene partner multiplex RT-PCR was performed. Total RNA was isolated from mononuclear cells from a peripheral blood sample using TRIzol reagent, then reverse transcribed with the SuperScript VILO cDNA Synthesis Kit. Multiplex RT-PCR was performed according to the protocol proposed by Burmeister *et al.* [8]. Amplified products were analyzed using a QIAxcel DNA high resolution cartridge. The results indicated *MLLT10* as a *KMT2A* partner gene. The observed amplicon contained a t(10;11)(p12;q23) translocation.

Treatment and outcome

Treatment included hydration, erythrocyte and thrombocyte transfusions, correction of acidosis and coagulation imbalances, empirical antibiotics and antimycotics. The patient received rasburicase and chemotherapy with low-dose Ara-C (0.5 mg/kg/day) on the basis of predominantly monocytic differentiation of the leukemic clone. Due to respiratory deterioration and progressive pulmonary hypertension re-intubation was necessary 4 hours later and the patient was referred to an intensive care unit for mechanical ventilation with nitrogen monoxide inhalation. After transient improvement with normalization of blood gas results, WBC dropped to $8 \times 10^9/l$ and lactate decreased from 12 to 8 mmol/l, and on the 3rd day the neonate became hypotensive. The Ara-C dose was increased to 1.0 mg/kg/day and continued until the 4th day of life. Despite continuous infusion of dobutamine, massive circulatory deterioration with recurrence of pulmonary hypertension and WBC increase to $76 \times 10^9/l$ occurred. On the 5th day of life, due to therapy resistance, persisting leucocytosis and progressive respiratory and circulatory insufficiency, the hospital ethics committee determined that it was permissible to withdraw oncological treatment. The neonate died a few hours later.

Discussion

Clinical presentation of our patient shares all the most common symptoms of CL [9-13]. Rearrangement of the *KMT2A* gene at chromosome 11q23 as the primary clonal genetic defect in the present case along with immunopheno-

type with dominant monocytic characteristics expressed by CD11c+/CD15+/CD33+/CD64+ also falls into a set of the most common features of CL [7]. However, co-expression of T-ALL-associated antigen CD3 suggested origin in a stem cell not fully committed to myeloid differentiation [7].

Translocation t(10;11)(p12;q23) identified in the patient accounts for approximately 10% of all *KMT2A*-rearranged AML cases and is the second most common translocation in pediatric *KMT2A*-rearranged AML [14]. It is mostly associated with subtype FAB M5, rarely reported in other AML subtypes, therapy-related AML, MPAL, and B-cell acute lymphoblastic leukemia (B-ALL). Association of this aberration with T-cell acute lymphoblastic leukemia (T-ALL) is reported extremely rarely [2, 15]. This recurrent rearrangement involves the *KMT2A* gene (alias *MLL*) on chromosome 11 band q23 with the *MLLT10* (previously called *AF10*) gene at 10p12 to produce the *KMT2A/MLLT10* fusion transcript [2, 16]. Unlike in translocations involving the majority of over 120 known *KMT2A* partners [17], *KMT2A* and *MLLT10* are in opposite transcriptional directions, which means that complex rearrangements with three or more breaks are often required to yield the functional fusion. Thus, combined cytogenetic, molecular and FISH analyses are necessary for an accurate diagnosis [18-20]. In the studied case the aberration affected not only the 10p12 locus but also a locus on the long arm of chromosome 10, while more precise clarification was unavailable. This translocation should be distinguished from other rare rearrangements known in infant leukemia fusing the *KMT2A* gene with genes localized in the close vicinity to *MLLT10*: *NEBL* or *AB11* [18, 21]. In a study of 756 children with *KMT2A*-rearranged AML, translocation t(10;11)(p12;q23) was established as an independent predictor of unfavorable prognosis with 5-year event-free survival (EFS) and overall survival (OS) of 32% each and probability of cumulative incidence of relapse of 52% [14]. However, the prognostic significance of this genetic entity may not be fully recognized due to molecular heterogeneity of the translocation and the small number of documented cases, including very sparse data on leukemia of neonates, which are presented in Table 1 [2, 22-24].

Leukemia with a blast population expressing antigens of more than one lineage is defined as MPAL and accounts for < 5% of pediatric leukemia cases [25]. MPAL *KMT2A*- (alias *MLL*-) rearranged is a separate entity according to the World Health Organization (WHO) classification with the incidence estimated at 12-18% of all MPAL cases in children [26]. There is strong molecular evidence that *KMT2A* abnormalities occur *in utero* and both *KMT2A* rearranged leukemia and MPAL may originate very early during hematopoietic differentiation from stem cells with bipolar lymphoid and myeloid differentiation potential [27]. Diagnosis of MPAL is based on a scoring system first published by European Group for Immunological Characterization of Acute Leukemias

Table 1. Summary of the clinicopathologic findings of three neonatal cases of *KMT2A/MLLT10*-positive leukemia reported in literature

Ref.	Age	Type of leukemia	Details of rearrangement	Diagnostic tools	Therapy	Outcome
[22]	0.04 yr	AML FAB M5	Insertion of 11q23 into 10p	FISH	AML MM-2000 protocol and auto-HSCT	EFS and OS 10.3 mo
[23]	ng	preB-ALL	Interstitial insertion of <i>MLLT10</i> gene into 11q23	Karyotyping FISH RT-PCR	AIEOP ALL 9502 protocol	EFS and OS 24 mo, severe cardiotoxicity
[24]	10 days	Intestinal myeloid sarcoma consistent with an undifferentiated leukemia with partial monoblastic differentiation	<i>KMT2A</i> rearrangement in intestinal infiltration <i>KMT2A/MLLT10</i> fusion transcript positive in bone marrow, while FISH negative for <i>KMT2A</i> rearrangement	FISH RT-PCR	Spontaneous remission of neonatal symptoms	at 5 months age full blown AML FAB M5 <i>KMT2A/MLLT10</i> -positive treated with allo-HSCT post AML BFM 2012 protocol; EFS and OS 9 mo

AML – acute myeloid leukemia, FISH – fluorescent in situ hybridization, RT-PCR – reverse transcription-polymerase chain reaction, EFS – event-free survival, OS – overall survival

Table 2. Summary of clinicopathologic findings of two neonatal mixed-phenotype acute leukemia (MPAL) cases reported in literature

	Ref. [25]	Ref. [6]
Type of publication	Study of 35 childhood MPAL cases in children	Case report
Age	2 days	10 days
History and clinical presentation	Not given	Twin, product of <i>in vitro</i> fertilization pregnancy, dermal nodules, peripheral facial nerve palsy
Immunophenotype	CD19, CD22, CD24, cyCD79a CD56 TdT CD11b, CD13, CD14, CD33, CD36, CD64, CD6	Bone marrow: (CD45) 85.4%, CD3 62.8%, CD5 63.7%, CD7 68.3%, and CD10, CD13, CD15, CD19, CD20, CD22, CD33, CD34, CD79a, CD117, Tdt, and HLA-DR negative; Skin biopsy: MPO positive and TdT/CD117/S-100 and CD1a negative
Type of MPAL	Bilineal B-lymphoid/myeloid	Bilineal T-lymphoid/myeloid
Cytogenetics	46,XY,t(9;11)(p13;q23)18/46,XY2	46,XX; FISH for 11q23 and chromosome 7 aberrations negative
Initial therapy	Standard protocol for AML	Interfant-99 protocol
Response	Non-responder	Not achieved
Additional therapy and outcome	Protocol for ALL → CR (MRD+) HSCT → toxic death, OS 0.4 yr	Toxic death at 15 th day of therapy

AML – acute myeloid leukemia, ALL – acute lymphoblastic leukemia, HSCT – hematopoietic stem cell transplantation, OS – overall survival, FISH – fluorescent in situ hybridization

(EGIL) and modified in 2008 to the WHO classification currently in force. Although according to the majority of publications cytoplasmic CD3 expression in a leukemic clone is a necessary marker of T-lineage involvement for MPAL diagnosis [25-27], according to the WHO, positivity of surface CD3 antigen is also its alternative approved indicator [15]. Therefore our case, diagnosed on the first day of life, is considered as a rare example of the T-lymphoid/myeloid subtype of MPAL t(v;11q23); *KMT2A* rearranged [15, 26] and supplements the first

description by Lou *et al.* of MPAL t(10;11)(p12;q23); *KMT2A/MLLT10*-positive in a 6-month-old infant [28]. Data on neonatal MPAL are almost non-existent. The data on the two cases are presented in Table 2. The prognosis in our case was difficult to predict; nevertheless, unfavorable factors were cumulated: leukemia at birth, mixed phenotype, high-risk genetic profile and generally severe clinical condition. No prospective, controlled trials exist to guide therapy either in CL or MPAL [29]. In MPAL it is usually started with AML-directed therapy or ALL-directed ther-

apy and switches if the initial treatment fails [27], though recently limited data have emerged suggesting that higher remission rates are achieved with acute lymphoblastic leukemia-like induction regimens. Allogenic bone marrow transplantation in first remission may be associated with improved survival compared with consolidation chemotherapy [29].

In conclusion, we have presented a case of a 1-day-old neonate with MPAL showing co-expression of myeloid and T-lymphoid markers and carrying complex translocation t(10;11)(p12;q23) with *KMT2A/MLLT10* rearrangement. It underscores that CL has to be included in differential diagnosis of neonates, requires in-depth immunophenotypic, molecular, genetic studies and remains a therapeutic challenge.

Acknowledgements

All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from parents of the patient.

The authors wish to thank Benigna Konatkowska for being an important contributor to the therapy of the patient.

The authors declare no conflict of interest.

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