doi: 10.48095/cctahd2025prolekare.cz20

Spontaneous remission of acute myeloid leukaemia

Spontánní remise akutní myeloidní leukémie

Baláž M., Faber E., Szotkowski T., Čerňan M., Papajík T.,

Department of Hemato-Oncology, University Hospital Olomouc
Faculty of Medicine and Dentistry, Palacky University Olomouc

SOUHRN: Akutní myeloidní leukémie (AML) je maligní onemocnění krvetvorby s vysokou mortalitou, které i přes pokroky v terapii zůstává obtížně léčitelné, zejména u starších komorbidních osob a pacientů s rizikovým genetickým profilem. Naprostá většina nemocných vyžaduje intenzivní léčbu, ke konsolidaci dosažené remise a vyléčení je často nezbytné provést alogenní transplantaci krvetvorných buněk. Přesto existují extrémně vzácné případy spontánních remisí AML, které mají většinou krátké trvání. V hypotézách o příčinném mechanismu spontánní remise je nejčastěji zmiňován imunitní efekt, v řadě případů navazující na infekci. Tato práce se zaměřuje na přehled dostupných kazuistik popisujících případy spontánních remisí za období 2004–2023. Celkem jsme identifikovali 27 případů u osob s mediánem věku 59 let (od 28 do 77 let), v 19 případech z toho šlo o muže. Nejčastěji šlo o AML typu M2 a M4, cytogeneticky byl nejčastěji popisován normální karyotyp. Délka spontánní remise se pohybovala od 1 do 120 měsíců s mediánem trvání 6 měsíců. Krátce popisujeme také vlastní zkušenosti s případem spontánní remise AML u 75leté ženy s cytogenetickým nálezem t(9;11)(p21;q23) a trisomie chromosomu 8, u níž spontánní remise trvá 48 měsíců.

KLÍČOVÁ SLOVA: spontánní remise – akutní myeloidní leukémie

SUMMARY: Acute myeloid leukaemia (AML) is a malignant haematopoietic disorder associated with high mortality, which remains challenging to treat despite therapeutic advances, particularly in older patients with comorbidities and those deemed high-risk. The vast majority of patients require intensive treatment, with consolidation of remission and potential cure often necessitating allogeneic haematopoietic stem cell transplantation. Nevertheless, spontaneous remission of AML is an extremely rare phenomenon, typically of limited duration. Hypotheses regarding the underlying mechanism of spontaneous remission frequently implicate an immune-mediated response, often subsequent to infection. This study reviews available case reports documenting instances of spontaneous remission between 2004 and 2023. In total, 27 cases were identified, with a median patient age of 59 years (range 28–77), of whom 19 were male. The most common AML FAB subtypes were M2 and M4, with a normal karyotype being the most frequently reported cytogenetic finding. The duration of spontaneous remission ranged from 1 to 120 months, with a median of 6 months. Additionally, we briefly report our own experience of spontaneous remission in a 75-year-old woman harbouring a cytogenetic abnormality t(9;11)(p21;q23) and trisomy 8, whose remission has persisted for 48 months to date.

KEY WORDS: spontaneous remission – acute myeloid leukaemia

INTRODUCTION

Acute myeloid leukaemia (AML) is a heterogeneous group of malignant haematological disorders arising from the transformation of a myeloid haematopoietic precursor, resulting in uncontrolled proliferation of leukaemic blasts. AML accounts for approximately 75–80% of all acute leukaemias in adults. The reported incidence is 3.7 cases per 100,000 persons per year and increases substantially with age, reaching up to 15 cases per 100,000 per year in individuals over the age of 70. The median age at diagnosis is 72 years, and epidemiological data indicate a slightly higher prevalence among men [1].

The prognosis of AML is determined by several key factors, including patient age, overall health status and associated comorbidities, and, most importantly, the genetic and molecular characteristics of the leukaemia. The five-year overall survival rate across adult patients of all groups and ages is 31.9 % [2]. Prognosis is significantly more favourable in patients younger than 60 years without major comorbidities who are eligible for intensive treatment. In low-risk AML, remission rates range from 80 % to 95 %, compared with 70–80% in intermediate-risk disease and 40–50% in high-risk disease. Long-term survival following intensive therapy is 60–70% in low-risk, 45–55% in intermediate-risk, and 15–20% in high-risk groups. By contrast, for patients ineligible for intensive treatment, the five-year survival rate is limited to 10–15% [1,3,4].

AML therapy is highly complex and involves either an intensive or a non-intensive approach [5]. Curative-intent strategies typically comprise intensive induction and consolidation chemotherapy, potentially combined with targeted therapy or allogeneic haematopoietic stem cell transplantation in selected patients. Non-intensive strategies include treatment regimens based on hypomethylating agents and inhibitors of the anti-apoptotic protein B cell lymphoma (BCL2), aiming to prolong the time to progression-free survival while maintaining a good quality of life. Palliative care approach focuses on cytoreduction and supportive measures.

Despite its aggressive nature and advances in drug development, AML remains a challenging disease to manage. Improvements in prognosis and long-term survival – particularly in the high-risk group – have been limited.

Nevertheless, spontaneous remission (SR) of AML has been observed in rare cases, occurring in the absence of any specific anti-leukaemic therapy. Although this is an exceptionally uncommon phenomenon, it has been documented repeatedly in the literature. The first reported case dates back to 1878, when regression of leucocytosis was observed in a patient following a severe typhoid infection [6]. To date, more than 100 cases of SR in AML have been reported. SR is usually transient and short-term, although exceptions do exist. According to available data, the median duration of SR is approximately 5 to 7 months [7,8], with exceptionally rare cases lasting several years [9]. SR is most commonly documented at the morphological level [7], however, cases of cytogenetic and molecular remission have also been reported [10]. Although SR is rare in AML, it represents a significant phenomenon, the underlying mechanism of which remains poorly understood. The immune response triggered by infection, often preceding SR, is considered the predominant factor [7]. To date, the Czech literature lacks a comprehensive synthesis of current knowledge and recent SR cases in AML; we therefore analysed published case reports to address this gap.

METHODS

For the purposes of this retrospective analysis, the PubMed database was searched to identify relevant case reports. The following keywords were used: "spontaneous remission" AND "acute myeloid leukaemia" and "spontaneous remission" AND "AML". Articles published between 2004 and 2023, which focused on adult patients and were available in English or Czech were included. Remission was defined morphologically by the presence of less than 5% blasts in the bone marrow. Eligibility for inclusion also required documented cytogenetic profiling of AML. The following parameters were assessed: patient age, sex, AML subtype according to the French-American-British (FAB) classification, cytogenetic and molecular genetic profile, event preceding SR onset, SR duration, depth of SR, and blood count parameters – number of leukocytes, platelets, haemoglobin. Additional data – specifically whether immunoglobulins or cytokine levels before or after SR were measured – were also evaluated where available. The data were analysed using Microsoft Excel.

RESULTS

A total of 27 cases were included in this analysis. Male patients predominated (19/27; 70.4%) compared with female patients (8/27; 29.6). The cohort ranged in age from 28 to 77 years, with a median age of 59 years. The most frequent AML subtypes according to the FAB classification were AML M2 and AML M4, each recorded in 5 (18.5%) cases. Secondary AML occurred in 4 cases (14.8%), one case each arising from myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML), essential thrombocythemia-type myeloproliferative neoplasm (MPN-ET), and one case of therapy-related AML (t-AML) following treatment for multiple myeloma.

Cytogenetic data were available for all 27 patients. A normal karyotype was the most frequently observed (10/27; 37.0%), followed a complex karyotype (4/27, 14.8%), trisomy of chromosome 8 (2/27, 7.4%) and translocation t (9;11) /2/27, 7.4%). Molecular abnormalities were reported in 12 patients (44.4%), most commonly including mutations in the isocitrate dehydrogenase 2 (IDH2) gene (3/27, 11.1%) and mutations in the nucleophosmin 1 (NPM1) gene (2/27, 7.4%). The complete available cytogenetic and molecular findings are summarised in Tab. 1. The blood count at diagnosis showed a median leukocyte count of 2.15×10^9/L (range: $0.2–240.0\times10^9$/L), a median platelet count of 84×10^9/L (range: $14–546\times10^9$/L) and a median haemoglobin value of 90 g/L (range: 37–133 g/L).

In the majority of cases, SR was preceded by an infectious episode (19/27, 70.4%). Pneumonia or other respiratory-tract infection were the most common (13/19, 68.4% of all infections), followed by soft tissue infections (2/19, 10.5% of all infections), gastrointestinal tract (GIT) infections (2/19, 10.5% of all infections), and, in one case each (1/19, 5.3% of all infections), sepsis or catheter-related bloodstream infection (CRBS).

Events other than infections also preceded the onset of SR. In 3 cases (3/27, 11.1%) this was solely the administration of transfusion product, while in 2 cases (2/27, 7.4%), no clear trigger was identified. SR in AML was also reported in 2 patients following discontinuation of lenalidomide, which had been administered as maintenance therapy for diffuse large B-cell lymphoma and multiple myeloma [11,12]. In 1 case (1/27, 3.7%), SR occurred after administration of a gonadotropin-releasing hormone (GnRH) agonist in a patient diagnosed with both AML and prostate cancer [13].

Overall, 13 patients (13/27, 48.1 %) received transfusion prior to SR onset, of whom 10 cases (10/27, 37%) had a con-

Tab. 1. Patient overview and case characteristics.

Author, reference	Sex, age	AML subtype (FAB)	Cytogenetic abnoramalities	Molecular-genetic abnormalities	Triggering event prior to SR	Duration of SR (months)
Fozza [8]	M, 72	M0 (secondary)	48 XY, del (6)(p22pter), +13, +14	not reported	infection, pneumonia	5
Müller--Schmah [9]	M, 61	M5a	t(9;11)(q22;q23), MLL/AF9	not reported	infection,CRBSI	120
Helbig [10]	M, 40	not reported	trisomy 8	BCOR +, RUNX1 +, IDH2 +	infection, soft tissue	6
Kremer [11]	M, 51	M4	c0omplex karyotype	not reported	discontinuation of medic-tion (lenalidomide)	5
MartínezDíez [12]	M, 71	not reported (secondary)	complex karyotype	JAK2 +, TP53 +, U2AF1+	infection, upper respiratory tract, discontinuation of medication (azctidine)	5
Tsavaris [13]	M, 64	M4 (secondary)	normal karyotype	not reported	GnRH agonist therapy	48
Kaźmierczak [14]	M, 77	M4	48 XY, + 13, +21	not reported	transfusion	7
Mozafiri [15]	M, 53	M4	normal karyotype	not reported	infection, pneumonia	18
Barkhordar [16]	F, 57	M2	11q23/KMT2A+, del(13q);	negative	infection, pneumonia	6
Xie [17]	M, 42	M5a	normal karyotype	not reported	infection, pneumonia	40
Trof [18]	M, 29	M2	t(8;21), del Y	not reported	infection, pneumonia	3
Trof [18]	M, 28	M5b	normal karyotype	not reported	infection, sepsis	consolidation therapy administered after achieving SR
Khalife-Hachem [19]	F, 52	M4	complex karyotype	IDH2 +, KRAS +	infection, pneumonia	not reported, patient died after achieving SR
Waller [20]	M, 66	not reported (secondary)	normal karyotype	CEBPA +	discontinuation of medica-tion (lenalidomide)	12
You [21]	M, 70	M2	normal karyotype	IDH2+, WT1+	infection, pneumonia	1
Grunwald [22]	M, 72	not reported	normal karyotype	NPM1 +	transfusion	12
Szotkowski [23]	F, 75	not reported	t(9;11)(p21;q23), MLL/AF9, trisomy 8	negative	infection, pneumonia	48
Hoshino [24]	F, 49	M5a	46,XX,t(8;16)(p11;p13)	MOZ–CBP+	no identifiable cause	4
Maywald [30]	M, 31	M5a	normal karyotype	not reported	infection, soft tissue	2
Rautenberg [32]	F, 59	M0	47,XX,+mar, t(4;12), WT1 overexpresion	WT1 overexpresion	infection, pneumonia	14
Al-Tawfig [33]	M, 47	M5b	normal karyotype	not reported	infection, GI tract	4
Marisavljevic [34]	F, 63	M2	46,XY,del(6)(q21)	not reported	transfusion	6
Teng [37]	M, 75	not reported	trisomy 8	not reported	infection, pneumonia	4
Zeng [38]	M, 31	M2	46,XY,t(8;21)(q22,q22), del(9)(q22,q34)	not reported	infection, pneumonia	2
Vachhani [39]	F, 73	M5	del (15 q)	NPM1 +, FLT3-ITD +	no identifiable cause	1
Bradley [40]	M, 58	not reported	normal karyotype	negative	infection, GI tract	24
Pachner [41]	F, 66	not reported	complex karyotype, trisomy MLL	not performed	infection, pneumonia	5

CRBSI – catheter-related bloodstream infection; F – female; GI tract – gastrointestinal tract; GnRH – gonadotropin releasing hormone; M – male; SR – spontaneous remission

comitant infection. In 1 patient (1/27, 3.7%), in whom transfusion was also the only documented event prior to SR onset, low-dose corticosteroids were additionally also administered [14]. Corticosteroids were given to a total of 4 patients (4/27, 14.8%) prior to SR onset, either as supportive care [8,14,15] or as part of the treatment of COVID-19 pneumonia [16]. Granulocyte colony-stimulating factor (G-CSF) was administered in one patient (1/27, 3.7%) [17].

The duration of remission was assessed in 25 of the 27 patients. In one case, consolidation therapy was initiated immediately after SR, with relapse occurring 4 later [18]. In the second case, SR duration was not reported, and the patient died shortly after remission [19]. Among 25 patients with a documented SR duration, the median was 6 months (range: 1–120 months). Molecular remission was achieved in 5 patients (5/25, 20%) [10,20–23]. Two patients received further treatment after SR, either consolidation therapy or bone marrow transplantation [21,24]. One patient developed another haematological malignancy, specifically blastic plasmacytoid dendritic cell tumour [17]. Müller-Schmah reported the longest documented case of SR, with a 2012 study describing follow-up of more than 10 years, during which minimal residual disease (MRD) in peripheral blood remained undetectable.

We describe the case of a 75-year-old woman diagnosed with AML characterised by t(9;11)(p21;q23), MLL/AF9 rearrangement, and trisomy 8. Due to severe comorbidities, a palliative symptomatic approach was adopted. At diagnosis, the patient developed severe infectious complications, including pneumonia caused by influenza A virus and septic shock of unclear aetiology. These complications were treated with oseltamivir and a combination of empirical antibiotics (ceftazidime, teicoplanin, and amikacin). Erythrocyte transfusions were also administered as part of supportive care. Following clinical stabilisation, the patient was transferred to hospice care, where the patient's condition unexpectedly improved. Two months later, the patient was re-evaluated in our department, and, unexpectedly, SR of AML was confirmed, with minimal residual disease (MRD) in the bone marrow undetectable. The patient continues to be monitored on an outpatient basis, with 48 months of follow-up at the time of publication.

In the reviewed literature, cytokine levels were documented in only one case following influenza A infection [21] and immunoglobulin levels were not reported in any case.

DISCUSSION

The pathophysiology of SR remains unclear; however, several hypotheses have been proposed. One of the leading theories suggests that immunological mechanisms are involved in SR induction. This is supported by the observation that the majority of reported SR cases were preceded by an infectious episode. In our analysis, infection prior to the onset of SR was documented in 70% of cases. Fever is present in over 90% of patients before SR [7]. SR has been associated not only with bacterial infections, most commonly pneumonia, but also fungal infections [25], Pneumocystis jirovecii[26], and viral infections such as influenza A [21] and COVID-19 [16].

Severe infections stimulate the immune system, leading to increased production of cytokines such as tumour necrosis factor-α, interferon-γ, interleukins 1, 2 and 6. These cytokines are believed to mediate the anti-leukaemic effect through activaction of immune effector cells, including cytotoxic T-lymphocytes, macrophages and natural killer (NK) cells [27–29]. In a 2012 study pertaining to a patient with MLL/AF9 rearrangement and long-term SR, *in vitro* analyses showed NK cells exerting cytotoxicity against the myeloid leukaemia cell line K562, accompanied by increased CD107a expression. The authors suggest a likely involvement of both humoral and cellular immunity in the occurrence of spontaneous remission (SR), with NK cell activity playing a key role in maintaining long-term remission [9]. A 2023 mouse xenograft model study demonstrated that infection with influenza A virus (subtype H1N1) slowed AML progression and also prolonged time of survival. It was also observed that in a patient with SR and influenza virus infection, the proportion of T-lymphocytes, particularly helper T-lymphocytes, was increased in peripheral blood [21]. However, more data are lacking in this aspect to support changes in cytokine production or changes in the immune profile.

Another immunogenic factor potentially contributing to SR is blood transfusion, which has been reported as a preceding event in several cases [30]. The proposed mechanism in this context involves cytokines and immune cells capable of eliciting a cytotoxic response or inducing an immune reaction analogous to the graft-versus-leukaemia effect [10,31]. In our cohort, there were also patients in whom no alternative triggering event preceding SR could be identified. In some cases, transfusion occured concurrently with infection, potentially amplifying immune activation and enhancing anti-tumour immunity. Of particular interest in this context is the case of a patient who experienced disease relapse after allogeneic bone marrow transplantation, without clonal evolution and with a decline in donor chimerism; however, following a severe episode of pneumonia, spontaneous remission occurred with restoration of complete donor chimerism [32]. Furthermore, cases of SR following the discontinuation of immunosuppressive agents, such as lenalidomide, suggest that the ensuing upregulation of immune activity may be sufficient to suppress the leukaemic clone.

Hypergammaglobulinaemia was also reported in patients experiencing SR; the overproduction of immunoglobulins may be driven either by infectious

stimuli or by immune responses directed against tumour-associated antigens [30,33]. In our patient cohort, however, immunoglobulin levels were neither assessed nor documented in any of the reported cases.

Regarding genetic factors, long-term SR lasting more than 10 years has been reported in patient with the t(9;11) translocation [9]. Another patient with a similar cytogenetic profile of AML [23], likewise achieved a durable, even molecular, remission. A separate publication describes a series of AML case reports involving NPM1 mutations and SR [35]; however, it is important to note that NPM1 mutations represent a relatively common AML subtype. Even in the presence of cytogenetic abnormalities typically associated with poor prognosis, such as complex karyotypes, SR may occur, as demonstrated in our analysis. Furthermore, data indicate that patients with normal karyotype (27%) showed a slightly longer median duration of SR, reaching 8 months (range: 1–40 months), compared to 6 months in the overall cohort. One case report described a female patient in whom SR was accompanied by clonal evolution and loss of the complex karyotype; repeated bone marrow examinations in this case also confirmed the presence of haemophagocytosis [19]. No consistent correlation between remission depth and cytogenetic profile has been established [10].

Our retrospective analysis supports and extends the findings of previously published studies summarising the current understanding of SR in AML. The most widely accepted hypothesis for its induction focuses on immune-mediated stimulation, activating the host's antitumour response. Infectious complications are common in AML, both at diagnosis and during treatment. Čerňan et al. reported that up to 93% of patients receiving induction therapy experience infectious complications [36]. Nevertheless, SR in AML remains an exceptionally rare clinical phenomenon.

CONCLUSION

At present, no definitive theory explains the occurrence of spontaneous remission in acute myeloid leukaemia, nor has any specific factor been identified that can reliably predict its onset or duration. A deeper understanding of the immunological mechanisms driving SR in AML could constitute a significant breakthrough in immunotherapy, particularly in improving its efficacy or enabling the development of novel immunomodulatory strategies. However, the rarity, unpredictability, and temporal variability of SR events make conducting prospective studies virtually impossible. Consequently, a comprehensive understanding of this phenomenon is likely to remain elusive in the near future.

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AUTHOR CONTRIBUTION

BM – preparation of the first draft and final version of the manuscript
FE, ST, ČM, PT – critical revision of the manuscript

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest in connection with the topic, preparation and publication of this study. Preparation of the manuscript was not initiated or supported by any pharmaceutical company.

ACKNOWLEDGEMENT

Supported by Internal Grant Agency of Palacky University (IGA_LF_2025_005) and Ministry of Health of the Czech Republic (MH CZ – DRO (FNOL, 00098892).

Submitted: 29. 4. 2025.
Accepted after peer-review: 20. 6. 2025.

Assoc. Prof. Tomáš Szotkowski, MD, PhD
Dept. of Hemato-Oncology
University Hospital Olomouc
Faculty of Medicine and Dentistry
Palacky University Olomouc
Zdravotníků 248/7
779 00 Olomouc
Czech Republic
e-mail: Tomas.Szotkowski@fnol.cz