Leukemia Research Reports 13 (2020) 100204

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Spontaneous remission of acute myeloid leukemia with NF1 alteration

Terrence Bradley[a,c,1], Radames Adamo Zuquello[a,1], Luis E. Aguirre (MD)[a], Nicholas Mackrides[b], Jennifer Chapman[b], Luisa Cimmino[c,d], Amber Thomassen[c], Justin Watts[a,c,*]

[a] University of Miami, Department of Medicine, Miami, FL, United States
[b] University of Miami, Department of Pathology, Miami, FL, United States
[c] Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, United States
[d] University of Miami, Deparment of Biochemistry and Molecular Biology, Miami, FL, United States

ARTICLE INFO

Keywords:
Acute myeloid leukemia
NF1 alteration
Clonal hematopoiesis
Spontaneous remission
Leukemoid reaction

ABSTRACT

Acute myeloid leukemia (AML) is defined by the presence of ≥ 20% myeloblasts in the blood or bone marrow. Spontaneous remission (SR) of AML is a rare event, with few cases described in the literature. SR is generally associated with recovery from an infectious or immunologic process, and more recently possibly with clonal hematopoiesis. We review the literature and assess the trends associated with SR, and report a new case of a 58-year-old man with a morphologic diagnosis of AML associated with a severe gastrointestinal (GI) tract infection. The patient had an NF1 variant that was previously unreported in AML as the only clonal abnormality. After treatment of the infection, the increased blast population subsided with no leukemia-directed therapy, and the patient has remained in a continuous, spontaneous complete remission for > 2 years.

1. Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease that is fatal in most patients. Without disease-directed therapy, essentially all patients will expire within weeks to months. Spontaneous remission (SR) of AML is a poorly understood and rare event, but it does occur, with multiple cases reported from the 1940's-present. SR is generally seen in the setting of acute infection, antibiotic use, or blood product transfusion, and an immune-mediated process has been postulated [1]. The time to relapse is generally short, with patients typically requiring standard treatment within a few months.

It is not clear if some SR cases, particularly the more durable ones, were actually a "leukemoid reaction", a non-malignant process characterized by an exaggerated immune response (usually to infection, e.g., *C. difficile colitis*) with marked leukocytosis and increased levels of pro-inflammatory cytokines and colony stimualitng factors (G-CSF/GM-CSF) [2,3]. Classically, there is mature neutrophilia in the absence of blasts [4].

In this letter, we present a novel case of AML with NF1 mutation that achieved a durable SR in the setting of GI septicemia. We review the entire body of literature on SR-AML, and analyze the charactetisitcis of SR-AML patients, including those with both brief and prolonged SRs.

2. Case presentation

A 58-year-old Hispanic man with a history of ankylosing spondylitis previously treated with methotrexate and infliximab developed fever, abdominal pain, and hematochezia during a trip to Central America. On return to the United States, blood work revealed 6% circulating blasts, hemoglobin 12.3 g/dL, white blood count (WBC) 2.2 × 10^3 cells/mm^3, 7% neutrophils, 45% lymphocytes, 4% monocytes, 19% eosinophils, and 2% myelocytes. Platelets were 546 × 10^3/mm^3. Bone marrow biopsy demonstrated 40-50% blasts, left-shifted myelopoiesis, and trilineage dysplasia. No Auer rods were seen. The blasts were positive for CD34, CD117, MPO, CD13, and CD33. Cytogenetics were normal. Molecular testing (11-gene AML next generation sequencing [NGS] panel) was negative. His anemia worsened and he required blood transfusions. Intravenous antibiotics were started.

The patient was transferred to our hospital with ongoing bloody diarrhea and hypotension. Computed tomography (CT) imaging showed acute colitis. Upon arrival his WBC was 14 × 10^3 cells/mm^3 with neutrophilia and no circulating blasts, hemoglobin was 7.6 g/dL (transfusion dependent), and platelets were 1,006 × 10^3/mm^3. Repeat bone marrow examination showed 25% blasts with background dysplasia (Fig. 1). AML induction was postponed as he was treated for GI septicemia.

* Corresponding author.
E-mail address: jxw401@miami.edu (J. Watts).
[1] These authors contributed equally and are co-first authors

https://doi.org/10.1016/j.lrr.2020.100204
Received 29 January 2020; Accepted 10 May 2020
Available online 16 May 2020

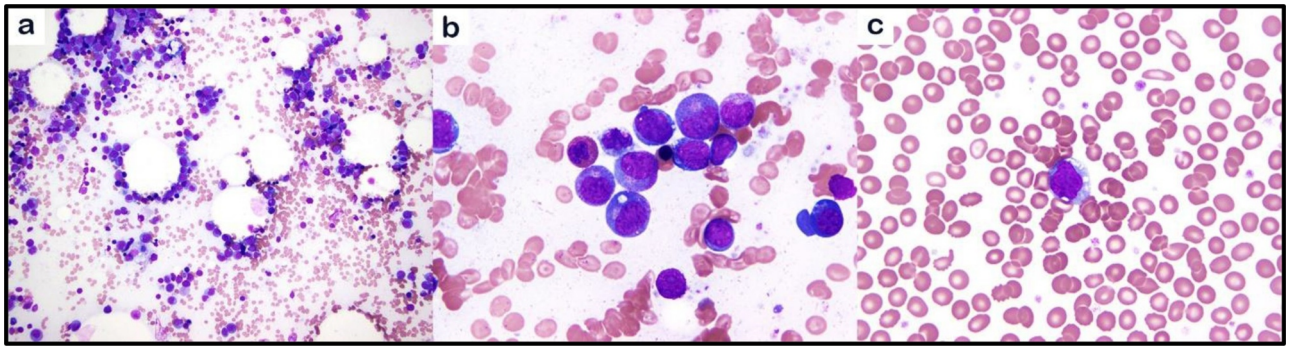

Fig. 1. Bone marrow biopsy showing acute myeloid leukemia. The bone marrow aspirate smears show left shifted myelopoiesis with increased blasts (a). Blasts comprise 25% of bone marrow cellularity (b), with circulating blasts in peripheral blood (c) (a, 200X, b,c, 1000x; a-c, May-Grünwald Giemsa stain).

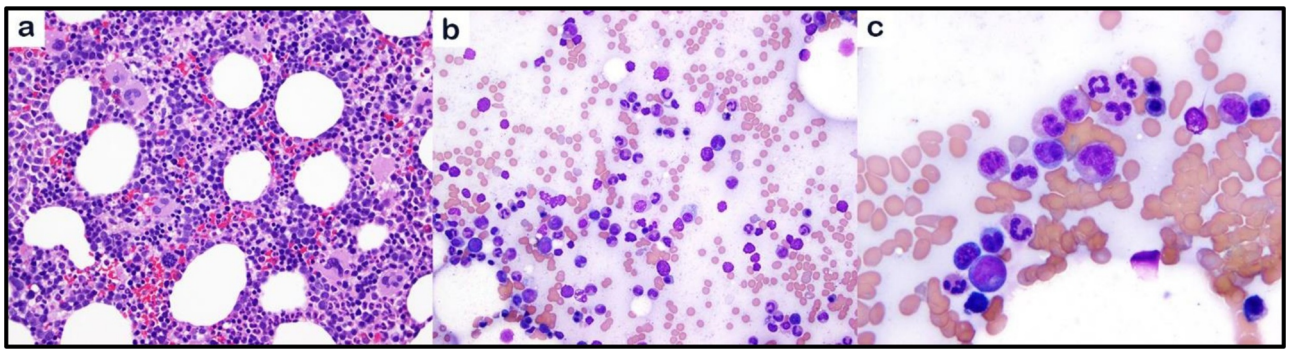

Fig. 2. Bone marrow biopsy with no evidence of acute leukemia. The bone marrow core biopsy shows hypercellular bone marrow with increased megakaryocytes (a). The bone marrow aspirate smears show maturing hematopoiesis (b) with no increased blasts (c) (a, 200X, H&E stain; b,c, 1000x, May-Grünwald Giemsa stain)

Over the next 2 weeks, the patient's symptoms resolved and his blood counts normalized. He underwent a third bone marrow biopsy ~4 weeks after the initial assessment (Fig. 2), which demonstrated a cellular bone marrow (50-70%), increased megakaryocytes, and mild dyserythropoiesis. Blasts comprised 1% of total cells. The only abnormality was an NF1 mutation (c.4430 + delT;splice-region) with variant allele frequency (VAF) 17% on an expanded NGS panel. Induction chemotherapy was deferred, and he was placed on observation.

Follow-up bone marrow biopsy 6 months after achieving SR demonstrated normocellular marrow (20-40%) with erythroid predominance and maturing trilineage hematopoiesis and no evidence of acute leukemia or myeloid neoplasm. NF1 gene reassessment could not be done due to insurance barriers. He remians in continuous SR for > 2 years at time of writing.

2.1. Analysis of reported cases

A PubMed search was performed using terms “acute leukemia”, “remission”, “regression”, “spontaneous”; including only articles written in English. Infant and down syndrome cases were excluded. A total of 47 articles were examined, containing 55 cases of acute leukemia with SR. Among the 56 cases studied (including our patient), 33 patients were male (59%) and 23 were female (41%). The median age was 53.5 years. AML comprised 50 cases (89%), acute lymphocytic leukemia 4 cases (7%), and cutaneous myeloid sarcoma 2 cases (4%).

The mean time to relapse was 12.4 months. The median time to relapse was 5 months (range 2 weeks-NE). Sixteen of 56 patients had SR for > 12 months (not including 1 patient who received therapy after SR and remained in CR > 30 months). Of these 16 patients, 10 relapsed and 6 remained in CR at time of publication. For the 6 patients without relapse, follow-up was 14 months, 18 months, 24 months (our case), 29 months, 4 years, and 10 years. Of these 6 durable CRs, all had monocytic differentiation (M4/M5) except our case (5/6 cases). Five received antibiotics for acute infection (the one that did not received a GnRH agonist for misdiagnosed prostate cancer). Three additional patients had late relapse > 2 years after SR. Of note, there were patients in remission for < 1 year at date of last follow-up, and their long-term outcome is unknown.

When looking at all 56 cases, almost half were monocytic subtype by FAB (M4/M5). Cytogenetics were available for 42 cases: 15 patients (36%) had a normal karyotype (NK), 5 (12%) trisomy 8, 5 (12%) t (8;21), 4 (9%) 11q23/MLL re-arragenemnt, 2 inv(16), and 2 t(3;3)/EVI1 re-arragenemnt. Ten patients (24%) had other abnormalities. More recently, Grunwald et al., reported an AML patient with NPM1 mutation who had SR with loss of NPM1 mutation, but persistent background mutations such as TET2. His disease relapsed abruptly ~1 year later, with recurrence of NPM1 mutation [5].

Patients were reported to have an associated infection in 76% of cases and blood product transfusion in 45%. Less common associations were G-CSF, steroids, hydroxyurea, termination of pregnancy, GnRH, tumor lysis syndrome, discontinuation of lenalidomide, and Henoch-Schönlein purpura. 9% had no identifiable association. Among 42 cases with a presenting infection, 45% had pneumonia (n = 19) and 16% bacteremia (n = 7). Other sources included upper respiratory, urinary, GI tract, skin, disseminated tuberculosis, and liver abscess.

3. Discussion

Our patient had histologic diagnosis of AML with > 20% myeloblasts on two subsequent marrow examinations. After treatment of concurrent GI sepsis, he entered SR and has been in continuous CR for 24 months. On review of SR in the literature, it is clear the vast majority of patients relapse, with most relapses occurring early (< 1 year). Patients were typically younger, de novo, and monocytic. Interestingly, most had a cytogenetic abnormality (e.g. + 8, core-binding factor (CBF) fusion, and MLL- and EVI1-rearragements; 36% had NK). Most patients with SR have an associated factor such as infection, but the causality has been opaque.

Table 1
Summary of our case and all cases reported in the literature

Year/ First author	Age/ Gender	FAB Subtype	Cytogenetics/Mutations	Associated factors or characteristic	Duration of remission
1. 1949 – Birge	33 F	AML-M5b	Not disclosed	Eclampsia, termination of pregnancy	22 months
2. 1979 – Lanchant	67 F	AML-M1	Not disclosed	Pneumonia	17 months
3. 1982 – Ruutu – 35	34 M	AML-M5b	Normal	Fever	2 months
4. 1985 – Ifrah	56 M	AML-M1	50 XXY, +4, +8, +14, +t(21q,22q), -21, -22	Disseminated tuberculosis, blood transfusion, leukocyte transfusion	34 months
5. 1986 – Jehn	34 M	AML-M4	Partial del(16)	Pneumonia, ear infection, blood transfusion	5 months
6. 1988 – Kizaki	53 F	AML – hypoplastic	Normal	Fever, antibiotic use	5 months
7. 1989 - Antunez de Mayolo	28 F	AML-M3	Aneuploidy (with extra chromosome in group C)	Fever, antibiotic treatment, blood transfusion	3 months
8. 1990 – Spadea	69 M	AML-M5a	Not disclosed	None	3 months
9. 1991 – Narayanan	64 M	AML-M4	46XY, del(5)(q13;q31)	Blood transfusion, *S. aureus* bacteremia	8 months
10. 1993 – Jimenez	72 F	AML-M0	3n hyperploid	Pneumonia, *S. epidermidis* bacteremia, blood transfusion, remote history of CHT for AML (ineffective)	5 months
11. 1993 – Kang	19 M	AML-M3	Not disclosed	Purulent cellulitis	7months
12. 1993 – Kang	19 F	AML-M3	Not disclosed	Tuberculosis pneumonia	14 months
13. 1994 – Paul	74 F	AML-M5	Two clones: {1}46XX, t(9;11)(p22;q23) {2}52XX, +3, +8, +8, +14, +19, +t(9;11) (p22;q23)	None	7 months
14. 1994 – Musto	49 F	AML-M5a	Not disclosed	Concomitant Henoch-Schönlein syndrome.	6 months
15. 1994 – Delmer	48 M	AML-M2	45 × 0, t(8;21)	Gram-negative and *Candida albicans* sepsis, blood transfusion	36 months
16. 1994 – Delmer	41 F	AML-M5	Normal	Prolonged fever of unknown origin, blood transfusion	14 months
17. 1994 – Delmer	54 M	AML-M2	Normal	Gram-negative sepsis, blood transfusion	3 months
18. 1996 – Mitterbauer	64 M	AML-M5b	Not disclosed	Sepsis, *E. faecium* bacteremia, hydroxyurea, blood transfusion	> 14 months
19. 1996 – Mitterbauer	83 M	AML-M2	t(8;21)(q22;q22) AML1/ETO, del(7)(q22)	Pneumonia, G-CSF, blood transfusion	1 month
20. 1997 – Takahashi	64 M	Unclear	Not disclosed	Pneumonia, G-CSF	4 months
21. 1997 – Takahashi	54 M	Unclear	47 XX, +8	Pneumonia, G-CSF	3 months
22. 1997 – Takahashi	70 M	Unclear	Not disclosed	G-CSF, blood transfusion	17 months
23. 2000 – Takezako	79 F	ALL-T	Not disclosed	Pneumonia, antibiotic use	1 year
24. 2000 – Martelli	26 F	AML-M4E	46 XX, inv(16)(p13q22), CBFB/MYH11 +	Interstitial pneumonia, antibiotics, hydroxyurea, blood transfusion	1 month (patient received CHT and relapsed 25 months later)
25. 2001 – Tzankov	60 F	AML – M1	Normal	Acute tonsillitis, pneumonia, G-CSF, blood transfusion,	10 months
26. 2001 – Shimohakamada	71 F	AML-M2	45 × 0, -1, +4(q31), t(8;21)(q22;q22), AML1/MTG8	Pneumonia, blood transfusion, high-dose methylprednisolone	4 months then lost follow-up
27. 2004 – Mayald	31 M	AML-M5a	Normal	Fever, group B streptococci bacteremia, antibiotic treatment	2 months
28. 2004 – Müller	61 M	AML-M5a	T(9;11)(q22;q23); MLL/AF9 fusion.	Fever, antibiotic treatment	> 29 months
29. 2004 – Fozza	72 M	AML-M0	48 XY, del(6)(p22-pter), +13, +14	Pneumonia, sputum positive for coagulase-negative *S. aureus* and *Candida spp*. Blood transfusion, steroids	5 months
30. 2006 – Tsavaris	64 M	AML-M4	Normal	GnRH agonist therapy	> 4 years
31. 2006 – Al-Tawfiq	47 M	AML-M5b	Normal	Perforated bowel, *Clostridium septicum* bacteremia	4 months
32. 2007 – Trof	29 M	AML-M2	45 × 0, t(8;21)	Infection, antibiotic use, blood transfusion	3 months
33. 2007 – Trof	28 M	AML-M5b	Normal	Beta-hemolytic Streptococci bacteremia, blood transfusions	Received consolidation CHT after SR. Relapse 4 weeks after SCT.
34. 2007 – Daccache	83 F	AML-M5b	47 XX, trisomy 8	Antibiotics for possible UTI; blood transfusion	2 weeks
35. 2007 – Hudecek	35 F	AML-M1	48 XX, del(3)(q21), +6, t(11;15)(q23;q15), +21. 11q23/MLL abnormality	Blood transfusion, prophylactic antibiotics	> 8 months
36. 2008 – Yoruk	4 F	T-ALL	Not disclosed	Fever, possible pneumonia versus upper respiratory infection	4 weeks
37. 2008 – Jain	66 F	AML-M4	Trisomy 8	*Candida* pneumonia	29 months
38. 2008 – Jain	72 F	AML-M5b	Not available	None	5 months
39. 2008 – Jain	46 M	AML-M5b	Not available	Liver abscess	2 months
40. 2009 – Chen	14 M	ALL-B	Normal	Pneumonia, tumor lysis syndrome, MRSA, *S. viridans* and coagulase-negative *Staphylococcus* in pleural fluid	14 days
41. 2009 – Marisavljevic	63 M	AML-M2	46XY, del(6)(q21)	Blood transfusion	6 months
42. 2010 – Teng	75 M	AML-M2	Trisomy 8	Blood transfusion, pneumonia	21 weeks

(*continued on next page*)

Table 1 (*continued*)

Year/ First author	Age/ Gender	FAB Subtype	Cytogenetics/Mutations	Associated factors or characteristic	Duration of remission
43. 2012 – Xie	42 M	AML-M5a	Normal	Pneumonia, G-CSF	Blastic plasmacytoid dendritic cell neoplasm 40 months after initial diagnosis
44. 2012 – Müller-Schmah	61 F	AML-M5a	t(9;11), MLL-AF9	Fever, *S. aureus* bacteremia, antibiotics administration	> 10 years
45. 2013 – Zeng	34 F	Cutaneous myeloid sarcoma	46 XX, normal	Blood transfusion, fever	1 month
46. 2013 – Zeng	31 M	AML-M2	46 XY, t(8;21)(q22;q22), del(9)(q22,q34)	Pulmonary infection by *Serratia marcescens*	2 months
47. 2014 – Adam	35 M	AML-M4	Not disclosed	Blood transfusion, possible infection	6 weeks
48. 2014 – Kazmierczak	77 M	AML-M4	48 XY, +13, +21	Blood transfusion, low dose steroids	7 months
49. 2014 – Purhoit	46 M	ALL-B	Normal	Acinetobacter spp. bacteremia, infective endocarditis, possible fungal pneumonia	9 weeks
50. 2015 – Takahashi	79 F	Aleukemic cutaneous myeloid sarcoma	Trisomy 8	No associated factor	2 months
51. 2017 – Hoshino	49 F	AML-M5a	46,XX,t(8;16)(p11;p13), *MOZ-CBP* fusion	None. Received BMT 4 months after SR.	4 months, at least.
52. 2017 – Kremer	51 M	AML-M4	45 XY, t(3;3)(q21;q26), der(17)t(17;21)(p11.2;q11;2)	Previous lymphoma / discontinuation of lenalidomide	5 months
53. 2017 – Mozafari	53 M	AML-M4	Normal	Pulmonary infection	> 18 months
54. 2018 – Höres	31 F	ALL	46XX, del(5)(q13;q22); *ACSL6* deletion.	Pregnancy, blood transfusion, GI infection	> 30 months (had SR but also received therapy)
55. 2019 – Grunwald	72 M	AML- M2	Normal, Mutated NPM1, RUNX1, NRAS, TET2, U2AF1, PRPF8	Blood transfusion, leukemia cutis	~12 months (relapsed)
56. 2019 – Bradley	58 M	Unclear (had MDS changes)	Normal; Deletion of NF1 gene	GI septicemia	> 24 months (f/u ongoing)

Of the 16 known patients with durable SR for >12 months, 6 (40%) have not relapsed. Of these 6, 5 had monocytic subtype and 5 had a concomitant infection at diagnosis. Three had a NK and 2 MLL-AF9 fusion (1 did not have cytogenetics available). This raises the question: are durable SRs attributable to: (1) driver-mutated AML undergoing SR via unknown mechanism (e.g. the MLL-rearranged cases), or (2) exaggerated, blastic "leukemoid reaction" in the setting of CH. Microbial products, such as endotoxin and nucleic acids, are potent stimuli for CSF production [6], and pharmacologic CSF exposure can induce a blastic marrow response [7].

Our patient presented with GI sepsis and hemorrhagic colitis, a known cause of leukemoid response [8]. Interestingly, he did not present with leukocytosis, the *sine-qua-non* of leukemoid reaction, but rather with leukopenia, although he did have a left-shift and marked thrombocytosis. Our patient's self-resolving blast increase and dysplastic features, normal cytogenetics, and long duration of SR, support that he may have had an atypical marrow stress response in the setting of isolated *NF1* mutation.

The *NF1* gene is a tumor suppressor and negative regulator of RAS. The canonical hereditary mutation is associated with neurofibromatosis Type 1, where the risk of myeloid leukemias is 200 – 500 times higher than the general population [9,10]. Somatic *NF1* mutations are found in ~5-7% of de novo AML, and are associated with poor prognosis [11–14]. Reports of high VAF and presence of the mutation in hematopoietic stem cells (HSCs) suggests that *NF1* may act as a driver or founder mutation in some AML patients and it is not a common CH gene [11,12,15]. *NF1* mutations occur throughout the gene and consist primarily of truncating frameshift mutations but also missense, nonsense, and indels with a recent hotspot mutation characterized in 27% of AML NF1 mutants at Threonine 676, which leads to nonsense-mediated mRNA decay [12]. The *NF1* mutation in our patient at c.4430+delT targets Arginine 1477 with a deletion causing frame-shift in a splice region, which would be expected to cause premature termination and truncated protein sequence lacking the c-terminal nuclear localization signal. Missense and splice mutations at R1477 in *NF1* have been previously identified in 7 patients with solid tumors and are predicted to be pathogenic (COSMIC); however, this is the first time it has been reported in AML.

We report a novel NF1 mutation in AML and one of the first cases of AML-SR with NGS data available. Whether our patient had self-limited blast proliferation/self-renewal in the setting of CH, or de novo AML with true SR, it is important to consider both possibilities when triaging leukemic patients presenting with intercurrent infection and reactive blood counts/unexplained count recovery. In the >50 cases we analyzed, while most SRs occured in the setting of severe physiologic stress, over half also had a recurrent cytogenetic abnormality (including 11 patients with AML-defining gene fusion), implicating an autologous mechanism than can induce remission in frank AML, although this is rarely durable, Table 1.

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