

An Indolent Course of Acute Myeloid Leukemia with Peripheral Spontaneous Remission in a 34-year-old Filipino Female

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Abstract

Background: Acute myeloid leukemia (AML) is a clonal, malignant disease of hematopoietic tissues, which carries a poor prognosis and a median survival of 12 months.¹ Definitive treatment includes chemotherapy and hematopoietic stem cell transplantation. Spontaneous remission in AML is possible but extremely rare, with 100 cases reported since the 1980s.^{2,3} Even rarer is an indolent course of de novo AML, with only eight patients reported in literature surviving beyond 12 months without treatment.³ To date, no case report of indolent AML has yet been published locally.

Objective: This paper reports the first documented case of acute myeloid leukemia following an indolent course who achieved spontaneous peripheral remission in the Philippines.

Case: A 34-year-old female presented initially with a three-month history of fever, pallor, dizziness and body malaise. Complete blood count showed pancytopenia and bone marrow aspirate with biopsy revealed acute myeloid leukemia. She required multiple transfusions and

developed severe sepsis secondary to osteomyelitis. After treatment with blood transfusion and antibiotics, the patient's blood counts improved and were maintained at almost normal levels for the next 16 months. Multiple repeat bone marrow biopsies still showed diffuse infiltration with acute myeloid leukemia. She remained asymptomatic, did not require further blood transfusions and did not undergo chemotherapy.

Conclusion: We report a rare case of an indolent acute myeloid leukemia in a young female patient who had spontaneous peripheral remission following a severe systemic infection. Despite abnormal bone marrow morphology and no chemotherapy, our patient has remained asymptomatic with normal blood counts 16 months since diagnosis of acute myeloid leukemia. To our knowledge, this is the first case report of indolent AML following spontaneous peripheral remission in the local setting.

Keywords: Indolent acute myeloid leukemia, spontaneous remission

Introduction

Acute myeloid leukemia is a clonal, malignant disease of hematopoietic tissues that is characterized by accumulation of abnormal leukemic blast cells in the marrow and impaired production of normal blood cells. Hence, marrow infiltration of leukemia is usually accompanied by anemia and thrombocytopenia, with a variable white blood cell count.¹

The prognosis of AML is poor. Before the introduction of chemotherapy, the median survival was approximately six weeks. However, even with the advent of chemotherapy, the overall median survival of patients is reported to be approximately 12 months.¹ Definitive management includes induction chemotherapy to induce remission. Once a remission is obtained, further chemotherapy or

hematopoietic stem cell transplantation are indicated to preserve the remission state.¹ Due to the aggressive nature of AML, chemotherapy is initiated as soon as the diagnosis is confirmed. This was supported by Sekeres et al., who found that the time from diagnosis to initiation treatment predicts survival in patients less than 60 years old.⁴ However, there have been rare occurrences of spontaneous remission in AML without definitive chemotherapy. Even rarer is an indolent course of AML. Only eight patients were reported in literature to have survived beyond 12 months without chemotherapy.³ Most of these reported cases were elderly patients, who opted supportive management rather than definitive chemotherapy. We hereby report a case of de novo AML in a young female patient who had an unexpected normalization of blood counts after recovery from severe infection. This was followed by a smooth course characterized by normal blood counts and bone marrow blasts more than 20% even after 16 months without chemotherapy. To our knowledge, this is the first case report of indolent AML following spontaneous peripheral remission in the local setting.

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Case

A 34-year-old female presented with a three-month history of pallor, dizziness, fever and body malaise. There was note of pancytopenia, with a haemoglobin of 6.8 g/L, white blood cell count of $1.42 \times 10^9/L$, neutrophils 9.0%, lymphocytes 84%, monocytes 7.0%, eosinophils 1.0%, and platelet count of $75 \times 10^9/L$. Blasts were not seen on peripheral blood smear. Bone marrow aspirate and biopsy revealed a cellular marrow with diffuse infiltration of myeloblasts, accounting for up to 50% of the cellular population (Figure 1). The patient was diagnosed with acute myeloid leukemia (AML) but did not consent to definitive chemotherapy. Her low blood counts required multiple blood transfusions with packed red cells and platelets.

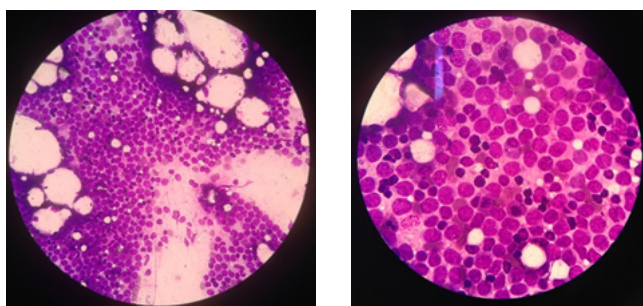


Figure 1. Bone marrow aspirate done March 2013 showing diffuse population of myeloblasts. A. High power view (40x magnification) B. Oil immersion view (100x magnification)

Three months after diagnosis, she was admitted due to fever and non-healing wound on the fourth digit of her left foot. The patient was noted to be hypotensive with blood pressure of 80/50 mmHg, tachycardic with a heart rate of 120 and febrile with a temperature of 38.5 degrees Celsius. Complete blood count revealed pancytopenia, with a hemoglobin of 62 g/l, white blood cell count of $0.62 \times 10^3/L$, absolute neutrophils count of 62, and platelet count of $32 \times 10^9/L$ (Table 1). Admitting impression was severe sepsis secondary to osteomyelitis of the left foot. Intravenous antibiotics (meropenem 1.0g every eight hours and clindamycin 300mg every six hours) and multiple blood transfusions were given. On the seventh day of admission, the patient became afebrile. Hemoglobin was maintained at 9.0 to 10 g/L and platelet count at 117 to $209 \times 10^9/L$ without further transfusions. Follow-up consultations after discharge revealed patient to be asymptomatic with normal blood counts.

Six months since the diagnosis of AML, the patient returned to our clinic still asymptomatic and with normal blood counts (Appendix). A repeat bone marrow aspirate and biopsy revealed a cellular marrow, still with diffusely infiltrating myeloblasts (Figure 2). The flow cytometry showed 29.81% blasts, showing moderately bright expression of CD45 and CD34, bright expression of HLA-DR, CD13, and CD33, but dim expression of myelomonocytic marker CD11c and cMPO, negative for monocytic marker CD14, B lymphoid

Table 1. Patient's complete blood counts since diagnosis and during admission for sepsis

	3.13.13	3.14.13	3.17.13	3.25.13	4.1.13	6.7.13	6.14.13	6.15.13	6.18.13	7.26.13
Hgb	68	66	102	124	113	107	62	97	96	133
Hct	18.9	20	21.8	37	35	29.5	17.9	29.5	28.7	37
RBC				2.00		3.79	2.22	3.62	3.32	
MCV				93	94	78	80.9	81.4	86.3	
MCHC					30	362	345	328	334	
WBC	1.42	3.2	1.46	3.91	1.7	0.62	0.68	1.02	1.02	3.5
Ne	9	41	11		8	10	30	25	22	43
Ly	84	57	77		88	65	70	53	64	49
Mo	7	2	10		4	5		9	4	
Eo	1		1			2		6		
Bo										
Plt	75	Normal	128	65	50	32	72	80	117	209
RDW										
Others	Retic: 1.7%		ANC = 161			ANC 62 Retic: 0.005%	ANC 204	Blast 7%		

Hgb, haemoglobin; hct, haematocrit; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; WBC, white blood cell; Ne, neutrophil; Ly, lymphocyte; Mo, monocyte; Eo, eosinophil; Bo, basophil; Plt, platelets; RDW, red cell distribution width

markers CD10, CD19, CD20, and CD22, T lymphoid markers CD3 and CD5, and NK cell marker CD56. Because of the persistence of leukemia despite normal peripheral blood counts, the patient was still advised chemotherapy to achieve complete hematologic remission. However, she was unable to comply again due to financial constraints and poor family support.

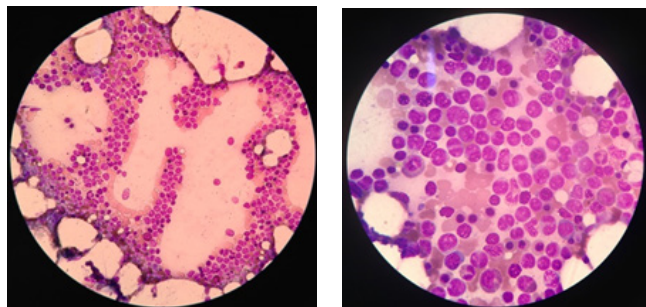


Figure 2. Bone marrow aspirate done September 2013 showing diffuse population of myeloblasts A. Low power view (10x magnification) B. Oil immersion view (100x magnification)

Fifteen months after diagnosis, the patient remained to be asymptomatic and did not require blood transfusion. A repeat bone marrow aspirate showed slight increase in myeloblasts to 39.86% (Figure 3). Fluorescent In-Situ Hybridization (FISH) was positive for t (8:21) in 3.74% of cells.

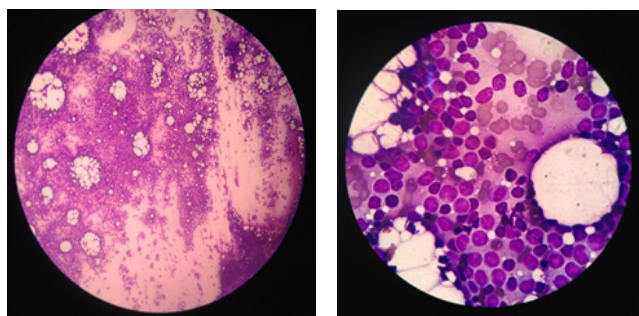


Figure 3. Bone marrow aspirate done May 2014 showing increased number of myeloblasts A. Low power view (10x magnification) B. Oil immersion view (100x magnification)

Discussion

Spontaneous remission in acute myeloid leukemia (AML) is extremely rare, with only 100 cases reported since the 1980s. Majority of the cases of spontaneous remission involved de novo acute myeloid leukemia,^{2,3} and with only three out of those 100 reported cases occurred in acute myeloid leukemia following myelodysplastic syndrome. Spontaneous remission is usually of short duration, with a mean of 7.7 months, after which relapse occurs and patients eventually expire after several months, with or without chemotherapy.^{2, 11}

According to Petti et al., spontaneous remission may be categorized into three types. First is peripheral spontaneous remission, characterized by normalization

of peripheral blood parameters (haemoglobin >11 g/dL, polymorphonuclear cells >1.5 x 10⁹/L, platelets >100 x 10⁹/L) with persistence of bone marrow dysplasia/marrow blasts. Second is morphologic spontaneous remission, described as normalization of all peripheral and bone marrow parameters (marrow blasts <5.0% with normal maturation of all cell lines) in patients with persistent cytogenetic abnormality. Third is karyotypic spontaneous remission, involving normalization of all peripheral and bone marrow parameters with disappearance of the cytogenetic markers.⁵

The exact mechanism for spontaneous remission of AML is not clear, although severe systemic infection and blood transfusions have been implicated. In the cases reported, it was observed that spontaneous remission was usually preceded by a severe systemic infection. In sepsis, there is an overwhelming increase in cytokine levels such as tumor necrosis factor α , interleukin-2, and interferon- γ . This exuberant activation of the immune system has been hypothesized to exert an anti-leukemic effect causing containment of the leukemia. Blood transfusions, on the other hand, could cause spontaneous remission of AML through the action of allogeneic lymphocytes and cytotoxic antibodies. These, in turn, could cause a graft-versus-leukemia effect similar to that of transplant patients. However, this hypothesis is controversial and further studies are needed to support it.^{6,7} Review of related literature did not yield recommendations or practice guidelines regarding management of patients with peripheral remission due to the rarity of this occurrence.

Spontaneous remission of AML was the initial consideration for this patient, due to the unexpected improvement in her cytopenias following sepsis. However, bone marrow examinations have repeatedly shown the presence of acute myeloid leukemia, despite the normal blood counts and clinically unremarkable course of the patient. An indolent clinical course without chemotherapy occurs even more rarely than spontaneous remission. Only eight patients were reported with smoldering AML who survived more than 12 months who did not undergo conventional chemotherapy. Reasons for deferring chemotherapy in these patients included: advanced age, presence of other co-morbid conditions, and patient's personal choice to receive supportive therapy instead.^{3, 8,10} In this case, chemotherapy was offered because the patient was very young, without known comorbidities, and showed persistence of leukemia in the bone marrow despite normal peripheral blood counts.

The known cases of indolent AML were elderly, in the range of 60-67 years of age.^{3,8,9,10} In contrast, our patient is relatively young at 34 years of age and followed an indolent course only after peripheral spontaneous remission. The unexpected normalization of her blood

counts following sepsis was consistent with spontaneous peripheral remission, but her bone marrow examination revealed persistent disease. Despite persistence of blasts in the bone marrow, our patient remained asymptomatic 16 months after diagnosis. To our knowledge, this is the first case report of indolent AML following spontaneous peripheral remission in the local setting.

Conclusion

Without definitive treatment, the survival of patients with acute myeloid leukemia is ordinarily measured in months. Spontaneous disappearance of leukemia occurs but is very rare. We report a rare case of an indolent acute myeloid leukemia in a young female patient who had spontaneous peripheral remission following a severe systemic infection. Despite abnormal bone marrow morphology and no chemotherapy, our patient has remained asymptomatic with normal blood counts 16 months since diagnosis of acute myeloid leukemia. To our knowledge, this is the first case report of indolent AML following spontaneous peripheral remission in the local setting.

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APPENDIX

	Feb 2013	3.13.13	3.14.13	3.17.13	3.25.13	4.1.13	6.7.13	6.14.13	6.15.13	6.18.13	7.26.13
Hgb	49	68	66	102	124	113	107	62	97	96	133
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Ly	75	84	57	77		88	65	70	53	64	49
Mo	12	7	2	10		4	5		9	4	
Eo	11	1		1			2		6		
Bo											
Plt	120	75	normal	128	65	50	32	72	80	117	209
RDW											
Others		Retic: 1.7%		ANC=161			ANC 62 Retic: 0.005%	ANC 204	Blast 7%		

	8.16.13	9.6.13	9.25.13	10.11.13	3.7.14	5.16.14	6.27.14
Hgb	154	148	155	146	144	163	136
Hct	46	44	44	39	42	49	41
RBC							
MCV							
MCH							
MCHC							
WBC	5.2	4.9	4.7	6.8	4.5	4.4	5.3
Ne	47	66	58	58	84	47	40
Ly	49	32	41	38	38	49	54
Mo	4	2	1	4	4	6	4
Eo					5		2
Bo							
Plt	226	225	203	181	192	150	163
RDW							
Others							

Hgb, haemoglobin; hct, haematocrit; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; WBC, white blood cell; Ne, neutrophil; Ly, lymphocyte; Mo, monocyte; Eo, eosinophil; Bo, basophil; Plt, platelets; RDW, red cell distribution width