

## CLINICAL VIGNETTE

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# Three Patients with Regression of CLL after Life-Threatening Illness

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### *Introduction*

Chronic lymphocytic leukemia (CLL) is one of the most common adult leukemias and is characterized by the proliferation of mature, CD5-positive, and monoclonal B-cells in the blood. While the course of CLL varies widely, many patients are asymptomatic and do not require treatment for years. Nevertheless, CLL is generally considered incurable and most patients require therapy as their disease progresses. There is great interest in developing therapeutic strategies to attain durable complete responses. Although spontaneous remission (SR) has been estimated<sup>1</sup> to occur in about 1% of CLL cases, examples are rarely published and remain poorly characterized. We describe three patients whose CLL regressed after different life-threatening events and briefly review the literature regarding spontaneous remissions in CLL associated with acute medical events.

### *Case Presentations*

Case #1 - A 65-year-old man with hypertension and asthma was diagnosed with CLL seven years ago. Fluorescent in-situ hybridization revealed deletions of chromosome arms 11q and 13q14. Considering his lack of symptoms and normal hemoglobin and platelet counts (15.4 g/dL and 303 x 10<sup>3</sup>/mL, respectively), he was followed without treatment. Although his WBC steadily increased over the next 3.5 years, reaching a peak of 60.88 x 10<sup>3</sup>/mL, he remained asymptomatic without treatment.

Three months later he was hospitalized with worsening hypoxemia and shortness of breath secondary to COVID-19 pneumonia. He had not received any COVID-19 vaccination and was initially treated with convalescent plasma, 10 days of remdesivir and dexamethasone, antibiotics, diuretics, prophylactic anticoagulation and prone positioning. His respiratory function gradually improved and he was discharged with home oxygen and rivaroxaban.

A CBC performed 1 month later showed that his WBC had fallen to within normal limits (7.59 x 10<sup>3</sup>/mL). His counts remained normal for the next 8 months, after which his lymphocytosis returned and has slowly progressed. He remains asymptomatic and requires no treatment.

Case #2 - A 61-year-old man was diagnosed with CLL 25 years ago. His past medical history includes coronary artery disease,

heart failure and mitral valve replacement. He was observed for 12 years without intervention. At that time, he developed marked lymphocytosis, anemia, thrombocytopenia, and fatigue, and started treatment with 4 cycles of fludarabine, cyclophosphamide, and rituximab followed by 2 cycles of rituximab alone. He had a 7-year remission before developing adenopathy, anemia, and fatigue and started on ibrutinib.

He responded well for 4 years until hospitalized for acute respiratory failure, worsening heart failure, and new atrial fibrillation. His ibrutinib was discontinued, he was intubated and underwent a transesophageal echocardiography-guided cardioversion, which showed perforation of his previously ligated left atrial appendage. His prolonged post-procedure course was complicated by mixed cardiogenic and septic shock, ventilator-associated pneumonia, acute kidney injury, anemia, and urinary retention. After 47 days in the hospital, he was discharged to a rehabilitation facility.

Despite not restarting ibrutinib for 27 months following his admission, his white blood count remained within normal limits. Peripheral blood flow cytometry drawn at the last follow-up identified a residual CLL population occupying 19% of the lymphocyte population. He continues to feel well and remains asymptomatic.

Case #3 - A 52-year-old female was diagnosed with CLL twenty years ago. Her past medical history includes hypogammaglobulinemia, aortic valve stenosis, paroxysmal atrial fibrillation, migraines, statin intolerance, nonobstructive coronary artery disease, and patent foramen ovale (PFO). For 15 years she was observed without treatment until developing progressive anemia, weakness, and fatigue. She was started on ibrutinib and responded well, with her white blood count decreasing to normal limits.

Two years ago, she stopped ibrutinib prior to PFO closure procedure. The procedure was complicated by a tear of her right common femoral artery, resulting in hypotension, SIRS, and a hematoma. Her condition stabilized following a thrombin injection and several blood transfusions.

Since discharge 28 months ago, her white blood count has remained within normal limits despite not restarting ibrutinib. Peripheral blood flow cytometry at her last visit showed a

residual CLL population (14% of lymphocytes). She remains asymptomatic and feels well.

### Discussion

We identified four articles describing patients with spontaneous remission that occurred after an event that might have contributed to tumor regression. In one study<sup>1</sup> Del Giudice et al. performed a microarray analysis of 8 patients with CLL SR and identified a distinct transcriptional profile notable for enrichment of B-cell receptor (BCR) signaling pathway components. A more recent study by Kwok et al.<sup>2</sup> of 20 CLL patients who underwent a complete or partial SR, excluded those with potentially associated medical events or therapies. Their results support a model of CLL SR in which previously dividing malignant cells enter a quiescent state and become hyporesponsive to IgM BCR stimulation.

No other studies comprehensively investigated determinants of CLL SRs. The literature largely consists of case reports with clinical history, tumor immunophenotype, and, if present, events potentially associated with the induction of the SR. Of the 4 case reports we reviewed, 3 occurred following acute infection<sup>3-5</sup> and 1 after myocardial infarction.<sup>6</sup> Our 3 patients CLL SR were previously hospitalized: for severe COVID-19; SIRS, and a mixed septic and cardiogenic shock. Nearly all of the reported cases of CLL SR were associated with conditions characterized by a heightened immune response, most commonly infection.

Interestingly, the enrichment of CLL SR among patients with a recent history of infection extends<sup>4</sup> to those infected with SARS-CoV-2. SR has been noted in unvaccinated COVID-19 patients with acute myelogenous leukemia,<sup>7</sup> follicular lymphoma,<sup>8</sup> NK lymphoma,<sup>9</sup> and Hodgkin lymphoma.<sup>10</sup> One hypothesis is that the relatively high frequency of SR in unvaccinated cancer patients with COVID-19 may be partially due to an exaggerated undetermined immune response favoring tumor elimination. However, whether infections or other medical events associated with CLL SR actually contribute to the remission has not been substantiated. Further research is needed, as investigation of CLL SR may identify biomarkers associated with indolent disease.

### REFERENCES

1. **Del Giudice I, Chiaretti S, Tavolaro S, De Propriis MS, Maggio R, Mancini F, Peragine N, Santangelo S, Marinelli M, Mauro FR, Guarini A, Foà R.** Spontaneous regression of chronic lymphocytic leukemia: clinical and biologic features of 9 cases. *Blood*. 2009 Jul 16;114(3):638-46. doi: 10.1182/blood-2008-12-196568. Epub 2009 Apr 22. PMID: 19387007.
2. **Kwok M, Oldreive C, Rawstron AC, Goel A, Papatzikas G, Jones RE, Drennan S, Agathangelou A, Sharma-Oates A, Evans P, Smith E, Dalal S, Mao J, Hollows R, Gordon N, Hamada M, Davies NJ, Parry H, Beggs AD, Munir T, Moreton P, Paneesha S, Pratt G, Taylor AMR, Forconi F, Baird DM, Cazier JB, Moss P, Hillmen P, Stankovic T.** Integrative analysis of spontaneous CLL regression highlights genetic and microenvironmental interdependency in CLL. *Blood*. 2020 Feb 6;135(6):411-428. doi: 10.1182/blood.2019001262. PMID: 31794600.
3. **Bülbül H, Nazlı HE, Olgun A, Togay A, Kahraman DS.** Spontaneous remission of chronic lymphocytic leucemia in a patient with SARS-CoV2. *Leuk Res Rep*. 2022;18:100336. doi: 10.1016/j.lrr.2022.100336. Epub 2022 Jun 30. PMID: 35789744; PMCID: PMC9242704.
4. **Thomas R, Ribeiro I, Shepherd P, Johnson P, Cook M, Lakhani A, Kaczmarek R, Carrington P, Catovsky D.** Spontaneous clinical regression in chronic lymphocytic leukaemia. *Br J Haematol*. 2002 Feb;116(2):341-5. PMID: 11841436.
5. **Bernard M, Drenou B, Pangault C, Dauriac C, Fauchet R, LePrisé PY, Lamy T.** Spontaneous phenotypic and molecular blood remission in a case of chronic lymphocytic leukaemia. *Br J Haematol*. 1999 Oct;107(1):213-4. doi: 10.1046/j.1365-2141.1999.01738.x. PMID: 10520243.
6. **Nakhla PS, Butera JN, Treaba DO, Castillo JJ, Quesenberry PJ.** Spontaneous regression of chronic lymphocytic leukemia to a monoclonal B-lymphocytosis or to a normal phenotype. *Leuk Lymphoma*. 2013 Aug;54(8):1647-51. doi: 10.3109/10428194.2012.753449. Epub 2013 Jan 2. PMID: 23185961.
7. **Kandeel EZ, Refaat L, Abdel-Fatah R, Samra M, Bayoumi A, Abdellateif MS, Abdel-Hady H, Ali M, Khafagy M.** Could COVID-19 induce remission of acute leukemia? *Hematology*. 2021 Dec;26(1):870-873. doi: 10.1080/16078454.2021.1992117. PMID: 34719343.
8. **Baptista RL, Moreira R, Rego E.** COVID-19 induced follicular lymphoma remission. *Hematol Transfus Cell Ther*. 2022 Apr-Jun;44(2):291-292. doi: 10.1016/j.htct.2022.01.017. Epub 2022 Mar 25. PMID: 35350272; PMCID: PMC8949839.
9. **Pasin F, Mascalchi Calveri M, Calabrese A, Pizzarelli G, Bongiovanni I, Andreoli M, Cattaneo C, Rignanese G.** Oncolytic effect of SARS-CoV2 in a patient with NK lymphoma. *Acta Biomed*. 2020 Jul 13;91(3):ahead of print. doi: 10.23750/abm.v91i3.10141. PMID: 32921739; PMCID: PMC7716983.
10. **Challenor S, Tucker D.** SARS-CoV-2-induced remission of Hodgkin lymphoma. *Br J Haematol*. 2021 Feb;192(3):415. doi: 10.1111/bjh.17116. Epub 2021 Jan 2. PMID: 33386647.