Could rituximab be a silver lining in refractory bone marrow fibrosis caused by lupus?

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that can present with a variety of clinical manifestations, ranging from mild skin involvement to multisystemic and severe central nervous system issues. While peripheral blood cytopenia is common in patients diagnosed with SLE, bone marrow involvement is very rare. Determining the cause of cytopenia in SLE is crucial for accurate diagnosis, effective treatment, and prognosis. SLE is characterized by immunological disorders, including T lymphocyte signal abnormalities and the pathological production of autoantibodies, influenced by various genetic and environmental factors. In SLE, the body loses immune tolerance to self-antigens. Antibodies against circulating T cells bind to the cell surface membranes of erythrocytes, leukocytes, lymphocytes, and platelets, resulting in tissue damage. This occurs through autoantibodies developed against cells, the complement system, or antibody-dependent cellular cytotoxicity. As a result, it induces cell death, cytopenia, and myelosuppression.¹

Most cytopenias in the SLE period resolve with disease control. However, in cases of persistent and long-term cytopenias, bone marrow assessment should not be overlooked.² The most common bone marrow abnormalities include hypocellularity, plasmacytosis, hemophagocytosis, dyserythropoiesis, and aplastic bone marrow. Myelofibrosis accounts for only 5%.³

In a patient with myelofibrosis, distinguishing between primary and secondary myelofibrosis is crucial as the treatment approaches differ. Unlike primary myelofibrosis, the detection of autoantibodies is crucial in autoimmune myelofibrosis, where no atypical cells are present in the bone marrow. The primary pathological distinction from classical myelofibrosis is the characteristic bone marrow reticulin fibrosis.⁴ SLE is the most common autoimmune disease associated with autoimmune myelofibrosis.⁵ In this regard, instances of similar cases are relatively rare in the literature. A recent article reported the detection of SLE-related myelofibrosis after observing pancytopenia in a 40-year-old female patient who presented with bleeding diathesis.⁶ According to an article published in 2018, a total of 45 cases of SLE-related myelofibrosis were documented in the literature.⁷

The initial treatment for SLE-associated myelofibrosis typically involves steroids, often resulting in a positive response.⁸ However, in cases where favorable results are not achieved or relapse occurs on dose reduction, alternative treatments become prominent. Second-line treatment with intravenous immunoglobulin has demonstrated clinically meaningful results.⁹ Other potential agents for SLE-associated myelofibrosis include azathioprine, mycophenolate mofetil, and cyclosporine.
In the cases documented in the literature, a treatment response is mostly achieved with these agents. However, there are just a few rare instances in which rituximab has been employed for the treatment of SLE-associated myelofibrosis due to its refractoriness to existing therapies. These cases hold promise for patients refractory to current treatments. From this perspective, it is noteworthy that rituximab, despite its potential for bone marrow depression, was successfully employed in the treatment of a patient with SLE-related myelofibrosis in 2019. Few cases of rituximab use for this purpose have been documented in the literature. Herein, a case of rituximab treatment for bone marrow fibrosis that developed in a patient diagnosed with SLE was discussed.

A 31-year-old female patient was referred from an external medical center in 2014 for the sudden onset of pleural effusion, refractory fever, and proteinuria. The family history revealed that the patient’s aunt was diagnosed with lupus. Initial laboratory tests at that time revealed the following: hemoglobin, 7.6 g/dL (normal range: 11.7-15.5 g/dL); leukocyte count, 5.9×10^3/uL (normal range: 4.4-11.3×10^3/uL); neutrophil count, 4.49×10^3/uL (normal range: 1.5-7×10^3/uL); platelet count, 41×10^3/uL (normal range: 150-400×10^3/uL). Antinuclear antibodies were positive with a homogeneous pattern, and anti-double-stranded deoxyribonucleic acid (anti-dsDNA) was also positive. Consequently, the patient was diagnosed with SLE, and treatment was started.

In 2015, mycophenolic acid was started due to persistent anemia and thrombocytopenia. However, the patient developed an allergy to mycophenolic acid; therefore, treatment was changed to azathioprine, methylprednisolone, dapsone, prednisolone, and hydroxychloroquine. The symptoms improved, and blood counts normalized. After a period of remission, the patient was reassessed five years later due to persistent cytopenia, with laboratory results showing a hemoglobin of 6.6 g/dL, a white blood cell count of 1.3×10^3/uL, a neutrophil count of 0.3×10^3/uL, and a platelet count of 42×10^3/uL. Antinuclear antibodies were positive with a fine nucleolar pattern, while anti-dsDNA was negative, and anti-SSA was positive. The patient presented with pale conjunctivae and marked malaise. A bone marrow biopsy was performed due to the profound cytopenia, which showed a hypercellular bone marrow with evidence of fibrosis and a Grade 2-3 increase in reticular fibers. This was interpreted as bone marrow involvement in SLE.

Intravenous immunoglobulin was started, along with hydroxychloroquine and methylprednisolone. However, there was no clinical improvement and cytopenia persisted. Consequently, we initiated off-label treatment with rituximab. Notably, the patient demonstrated significant improvement in pancytopenia six months after rituximab therapy.

Subsequent follow-up examinations after rituximab treatment showed a hemoglobin level of 12.2 g/dL, a white blood cell count of 5.18×10^3/uL, a neutrophil count of 2.96×10^3/uL, and a platelet count of 187×10^3/uL. These values were measured at a 2-g dose during the 26-week follow-up. The patient responded well to rituximab treatment and achieved a complete response. The patient has been on rituximab therapy for three years and is still closely monitored for remission.

Rituximab is an anti-CD20 monoclonal antibody. When used in autoimmune diseases, it binds to the CD20 protein, slowing down tissue damage by suppressing humoral immunity. The use of rituximab in SLE has not been definitively established. Conversely, rituximab itself may lead to myelosuppression. In this particular scenario, the myelosuppressive effects of rituximab on the bone marrow, coupled with limited research and understanding of myelosuppression treatment in SLE, led to significant confusion.

Regarding relapse after rituximab, a literature review revealed that relapses typically occur between 6 and 18 months following treatment. Remarkably, our case has maintained remission for three years. Rituximab proved to be a life-saving intervention in our patient’s case, as it...
effectively addressed the challenges faced by a young individual who had failed to respond to conventional treatment options. In conclusion, the use of rituximab proved beneficial in treating the bone marrow fibrosis associated with SLE. Similar to our experience, a limited number of other studies in the literature have demonstrated remarkable results. However, more detailed research and additional experience are required for the treatment of myelofibrosis caused by SLE.

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