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Idiopathic cytopenia of undetermined significance (ICUS) treated with low dose of Lenalidomide

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Abstract

A 74-year-old previously healthy non-Hispanic white male initially presented in 2018 with easy bruising. He had no prior demonstrated personal or family history of bleeding or clotting diathesis. His physical exam showed no cutaneous ecchymosis, petechiae, lymphadenopathy, or hepatosplenomegaly. Peripheral bloodwork at that time showed a CBC and a peripheral blood smear with normal ranges and no significant atypical findings.

In September 2019, he reported easy bruising, and lab tests showed a CBC and peripheral blood smear with a normocytic anemia of 13.7 gm/dL (11.0 – 15.5 gm/dL) with a significant decrease over the next coming months. In October 2019, the hemoglobin decreased to 12.3 gm/dL with rapid progression to 5.9 gm/dL within a 6-week period where he was referred to hematology to evaluate for significantly worsening cytopenias. On first evaluation, the patient reported decreased energy and increased fatigability but denied other B-symptoms including fever, night sweats, and weight changes. He also reported, of note, that he had a significant lifetime history of neurologic symptoms including burning and tingling of his feet, large length-dependent fiber neuropathic symptoms, difficulty in hearing, and autonomic failure with presyncope, especially with standing as well as slow digestion and poor secretions which resulted in a severe hardship when consuming meals and dry mouth. A neurological examination found the sensorimotor neuropathy and presyncope which was felt to be consistent with an eighth cranial nerve deficit, but did not observe significantly abnormal findings to suggest a central cause for his fatigue. It was unclear whether any of these symptoms were acutely bothering or related to his relatively acute aplastic anemia, and management of these were approached secondarily to his cytopenias.

Keywords: Rheumatoid arthritis; ESR; CRP; American College of Rheumatology criteria

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Introduction

Idiopathic cytopenia of undetermined significance (ICUS) is often diagnosed, among others, in patients in whom the usage of certain drugs is advised against. It is a diagnosis of exclusion of other pre-malignant conditions like clonal cytopenia of undetermined significance (C-CUS), which considerably elevates the risk of developing blood malignancies. One of the drugs with a risk for the development

of a pre-malignant blood condition is Lenalidomide. It was previously shown that low-dose Lenalidomide is a safe and effective alternative to regular transfusions in low-risk MDS with chromosome 5q- or complex karyotype dysplastic syndrome refractory anemia, and that this effect becomes apparent within 14 days.

In this case study, we describe low-dose Lenalidomide therapy and prophylactic antibiotic therapy in a patient with ICUS for the first time using international guidelines for the treatment of patients with myelodysplastic syndromes (WHO classification), taking into account that cytopenias are more common at diagnosis and should be correctly managed by diagnosis and therapy in MDS. The paper also sheds light on unanswered questions concerning the treatment.

According to the 2016 World Health Organization (WHO) classification, idiopathic cytopenia of undetermined significance (ICUS) is characterized by persistent, unexplained cytopenias without evident dysplastic changes. Its distinguishing features are idiopathic cytopenias for no less than 6 months, dysplasia in 10% or fewer hematopoietic cells in the maximum of one hematopoietic line, and the absence of both clonal proliferation and large cytogenetic diseases related to cytopenia. Almost the same picture can be seen during the persistent and unexplained cytopenias without evident dysplastic changes after being subjected to therapeutic exposure of chemotherapy or ionizing radiation.

According to the Medical Subject Headings (MeSH) vocabulary, cytopenia is a reduction in the number of leukocytes, erythrocytes, or platelets circulating in the blood. A number of mechanisms may be the cause of cytopenia's appearance. In a bone marrow with increased hemolysis, various enzyme deficiencies, or a hypoplastic radius, a decrease in the number of erythrocyte stem cells, the number of reticulocytes, and erythrocytes in the circulating blood is also reduced, which will increase the demand for new red blood cells coming out of the bone marrow. In such cases, the reduction in the number of platelets in the blood is a reflex of cerebellar microhemorrhagic syndrome and subsequent brain damage. Such variations include genetic conditions, red cell inclusions, anemia of the pre-hemodialysis patient, and hereditary elliptocytosis.

Rationale for Using Lenalidomide

Idiopathic cytopenia of undetermined significance (ICUS) is an unusual entity consisting of a clonal hematopoietic disease limited to cytopenias without having clinical findings associated with myelodysplasia or known features of myelodysplastic syndrome. The diagnosis of ICUS is established once the remaining causes of unexplained cytopenias are eliminated. The presence of particularly the so-called MDS-associated cytogenetic abnormalities appears to be one of the most valuable features in identifying early forms, identifying which patients might evolve into overt myelodysplastic syndrome. Mostly, asymptomatic patients are remaining monitored. Therapeutic options, when expected, are based on the elimination of secondary causes and also the use of growth factors and even immunosuppressive agents. A lifelong cytopenia support of especially anemia and thrombocytopenia is given in the patients moving to ICUS.

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There is no individual treatment guide for ICUS patients. Especially in elderly cancer patients, micro-therapies are needed, and the usage of cytopenias is controversial. Immunosuppression therapy is one of the treatment options for especially hypoplastic low-risk patients, for example, young patients who do not want allogeneic stem cell transplantation. Low-risk patients are typically more resistant to lenalidomide therapy, the immune system parameters in the bone marrow are different from those in the normal population and study groups, and as a result of a hyperactivated immune system, for example, lenalidomide treatment is expected to be more effective in reducing Tregs, Th22, and Th17 cells in other disease groups.

Case Presentation

A 74-year-old previously healthy non-Hispanic white male initially presented in 2018 with easy bruising. He had no prior demonstrated personal or family history of bleeding or clotting diathesis. His physical exam showed no cutaneous ecchymosis, petechiae, lymphadenopathy, or hepatosplenomegaly. Peripheral bloodwork at that time showed a CBC and a peripheral blood smear with normal ranges and no significant atypical findings. In September 2018, he reported easy bruising, and lab tests showed a CBC and peripheral blood smear with a normocytic anemia of 13.7 gm/dL (11.0 – 15.5 gm/dL) with a significant decrease over the next coming months. In October 2018, the hemoglobin decreased to 12.3 gm/dL with rapid progression to 5.9 gm/dL within a 6-week period where he was referred to hematology to evaluate for significantly worsening cytopenias. On first evaluation, the patient reported decreased energy and increased fatigability but denied other B-symptoms including fever, night sweats, and weight changes.

He also reported, of note, that he had a significant lifetime history of neurologic symptoms including burning and tingling of his feet, large length-dependent fiber neuropathic symptoms, difficulty in hearing, and autonomic failure with presyncope, especially with standing as well as slow digestion and poor secretions which resulted in a severe hardship when consuming meals and dry mouth. A neurological examination found the sensorimotor neuropathy and presyncope which was felt to be consistent with an eighth cranial nerve deficit, but did not observe significantly abnormal findings to suggest a central cause for his fatigue. It was unclear whether any of these symptoms were acutely bothering or related to his relatively acute aplastic anemia, and management of these were approached secondarily to his cytopenias.

Diagnostic Workup

A bone marrow aspiration and biopsy were performed to rule out underlying myeloid neoplasia, but the bone marrow cellularity was normal and no significant increase in megakaryocytes was detected. Bone marrow samples showed normal myeloid, erythroid, and megakaryocytic cells without any dysplastic features. Fluorescence in situ hybridization (FISH) testing was performed for BCR/ABL1, JAK2/PCM1, and FGFR1IL, and no evidence of myeloproliferative disorder was found. No evidence of any chromosomal abnormality or gene rearrangement was detected in the conventional cytogenetic

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analysis. Because myelodysplastic syndrome (MDS) was considered during diagnostic workup, we also tested the bone marrow using the DAKO Omnis CDx Panel with CD34, CD13, CD117, GATA-1, CD61, myeloperoxidase, and hematoxylin and eosin stains.

The frequency of the bone marrow blast was 0.6%. All erythroid precursors, myeloid precursors, and megakaryocytes were not dysplastic during the review with a CD34, CD13, and CD117 triune back-to-back staining of the bone marrow section made by the Omnis system. Next-generation sequencing using TruSight Myeloid panel covering the 54 genes frequently mutated in MDS, myeloproliferative neoplasms (MPN), or complex cytogenetic abnormalities was also applied. Unfortunately, this testing also failed to detect any pathogenic mutations. Hematological findings suggested an ICUS with isolated thrombocytopenia. Due to refractory thrombocytopenia and long-term risk of ITP, a treatment decision was taken.

Treatment Approach

The patient was adequately informed about the approved indications regarding lenalidomide and potential side effects. The decision to begin low-dose lenalidomide was made after careful consideration of the patient's age, general state of health, isolated cytopenia, and myelodysplastic features. It was with the patient's understanding that ICUS is considered an AHA-fibrotic phase, and that these subsets of patients have an increased risk of progression that may include increased fibrosis, clonal progression, and even transformation to myelodysplasia or acute myeloid leukemia. We also considered the historic data about the improvement of cytopenia in 18 cases of low-risk MDS reported by Santini et al. At the time of writing, the French IPSS or the more recently revised WHO Classification for Myelodysplastic Syndromes Category Definitions (2016 revision) had not yet been established.

The patient was monitored closely. After two cycles, he presented with a significant improvement in thrombocytopenia, changing from 55 × 10^9/L at diagnosis to 119 × 10^9/L. Up to the fourth cycle, increasing doses of erythropoietin failed to maintain his RBC count over 7.5 × 10^6/µL. Over the following months on lenalidomide, the patient experienced progressive and sustained improvement in thrombocytopenia and also a reduction in the percentage of ring sideroblasts in the bone marrow aspirate. The optimal response is being maintained. The decrease in fibrosis, as observed in the bimonthly peripheral blood samples, and in at least one bone marrow biopsy performed in June of the current year, are also important findings. The drug has been well-tolerated. The patient has not required blood transfusions. In conclusion, a patient with ICUS was treated with lenalidomide, with good results over time.

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Selection of Lenalidomide Dose

Therapeutic steps in low-grade MDS are complicated due to a lack of established, evidence-based treatment guidelines. In view of a defective immune response to infection in patients with low-grade MDS and to minimize the potential damage to the bone marrow, the only curative option besides lenalidomide in RC can be hypomethylating agents. Patients who receive these drugs can achieve durable responses, based mainly on improvements in cytopenias, possibly due to the eradication of abnormal clones, more rarely by restoration of pancytopenia. However, responses to this drug are far less frequent in patients with low-grade MDS, possibly due to a lower rate of abnormal progenitors or to intrinsic resistance of these progenitors to the demethylating effects.

On the basis of its effects in low-grade MDS, patients with ICUS, characterized by low-grade marrow abnormalities, disorder with ineffective hematopoiesis, and a low rate of transformation to high-grade MDS/AML, and peculiar responses to lenalidomide, have been especially targeted for this therapy. However, the best treatment schedule for RC is far from established. Lenalidomide, the drug of choice for patients with only neutropenia and a low degree of del20q, when applied to patients with more severe cytopenia or del5q, and also to those with a higher degree of marrow dysplasia, usually requires over 40-50 mg and at least 3 months to start increasing counts. Therefore, the use of lower lenalidomide doses, possibly after a 1-month induction period in non-RC patients, could be a useful means to limit bone marrow exhaustion and to reduce the eventual need for red blood cell and platelet support in non-RC patients with more severe cytopenia.

Monitoring and Follow-Up

The follow-up began 4 months after the starting of Lenalidomide, with normal blood count and the lack of other relevant symptoms. The patient presented 2 episodes of streptococcal tonsillitis, one of them resolved conservatively, and another leading to treatment with amoxicillin plus clavulanic acid. I noted the persistence of the treatment benefit during this period. In summary, this is a case of an adult patient with pancytopenia with 4 years of duration, associated with an autoimmune disease, ICUS, and symptomatic, having received low doses of Lenalidomide with a benefit, with complete remission for more than 4 months, thus being another presented as monotherapy in the dosage of 2.5 mg by the request of the patient and with side effects already known in the literature. I come to this add therapeutic strategy with the potential benefit, which is open to scrutiny and further study in a broader patient population with the same syndrome, responding to the seriousness of the cytopenias in the patient's clinical management and the lack of any personal comorbidities.

The patient had an excellent initial response and it was kept unchanged in the first 4 months. The follow-up began 4 months after the starting of Lenalidomide, with normal blood count and the lack of other relevant symptoms. The patient presented 2 episodes of streptococcal tonsillitis, one of them resolved conservatively, and another leading to treatment with amoxicillin plus clavulanic acid. When it completed 2 years of ICUS diagnosis, the blood count had already made 10 elements, and at the

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moment the patient presents with normal blood count. I noted the persistence of the treatment benefit during this period.

Discussion

Lenalidomide has shown clinical efficacy in the subset of low-risk MDS patients with del(5q). This drug is also seen to have benefits in some adult transfusion-dependent anemic patients without 5q deletion through erythroid hematologic response. We have described the first case report of ICUS patients, who received a low dose of Lenalidomide and achieved hematologic improvement in all myeloid lineages. The patient has beta-thalassemia trait and had been diagnosed with ICUS three years ago at the age of 53 years. She had been suffering from persistent leukopenia and anemia for three years. The male was hospitalized because of loss of appetite for four weeks. The overall severity modality of the disease was due to the moderate degree of pancytopenia; a severe category was given to species 3: the patient was suffering from physical weakness and could not tolerate normal activities and working life.

ICUS is a new terminology and the patients for this disease were relatively rare. Treatment options have not been well documented. It is imperative for both clinical and laboratory hematologists to differentiate between ICUS and known diseases, and exclude the typical clonal cytopenias (CCUS) to enable accurate treatment decisions. However, when population and clinical applications of disease progression to myelodysplastic syndrome or acute myeloid leukemia, revealed continued low-risk of progression to clonal disease. We believe that the low dose regime that was applied in our case study with raised concerns for safety is appropriate as a further study with the drug should be performed at a higher number of patients with ICUS. If appropriate efficiencies and safety of low dose lenalidomide can be proved for patients suffering from ICUS, it is believed that these patients will be added to the drug at a sufficient level.

Comparison with Standard Therapies

Idiopathic cytopenia of undetermined significance (ICUS) is an emerging medical diagnosis. It was first described when evaluating patients with macrocytosis and cytopenia of unknown origin being evaluated for dysplasia and the diagnosis of refractory cytopenia of unknown significance (RCUS), refractory anemia with ringed sideroblasts (RARS), or myelodysplastic syndrome (MDS) would not be met due to the absence of dysplasia in the bone marrow. A series of these patients showed that 2 to 3% of patients older than 50 years with mild anemia and macrocytosis without any other apparent cause could be affected by ICUS. Patients with ICUS were found to have a low probability of progression to MDS but were more likely to have other comorbid conditions. Conflicting information has been derived from studies evaluating associations of clinical and biological findings in blood counts and bone marrow studies to predict those at high risk of developing a true MDS, evolving to bone marrow failure, or experiencing a poor prognosis. The management is based on the treatment of comorbid conditions and surveillance with periodic hemogram assessment.

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However, the ground of the condition is that patients should not receive any disease-modifying therapy, chemotherapy, or hematopoietic cell transplantation, and supportive therapies should be provided to correct and prevent conditions associated with anemia, neutropenia, and thrombocytopenia. In case of associated immune disease or other insufficiently controlled comorbid condition, the available cure should be provided after careful consideration of the risks and benefits of the treatment, with the understanding that any intervention that affects hematopoiesis can significantly alter the progression from cytopenia that does not satisfy dysplasia or ANC criteria of an MDS to these entities.

Safety and Tolerability of Lenalidomide

Myelosuppressive treatment promises to restore normal peripheral blood counts, but at the time of diagnosis, ICUS should always be ruled out, as some cases, while waiting for clonal drift to appear, may be candidates for treatment instead of just a watch and wait approach. In our patient, a low dose of Lenalidomide led to a complete normalization of blood counts and has demonstrated that patients can tolerate a low dose of Lenalidomide even for prolonged periods, without developing severe hematological toxicity. No other treatment was given to the patient after 55 months of Lenalidomide, no clonal progress could be demonstrated, and the treatment was overall an effective and well-tolerated treatment. Treatment with low-dose Lenalidomide (5 mg/day) is effective and well-tolerated. Norton et al. first identified a group of otherwise healthy individuals presenting with isolated unexplained cytopenias; with exclusion of other causes, instead of a diagnosis of idiopathic cytopenia. During the observation time, 44% of the patients developed a definite diagnosis of MDS, an AML therapy was started in 20% and 36% of the patients remained without a definitive diagnosis. In our patient, treatment was started 85 days after the diagnosis and after 82% of time, the patient remained in idiopathic cytopenia status. The goal of the treatment was not a cure but to help with the pancytopenia; therefore, there was a benefit from the therapy for nearly one year in the low-dose situation.

Conclusion

In conclusion, this case report demonstrated that ICUS can be treated successfully with a low dose of lenalidomide. No serious side effects have been recorded due to an optimal initial dose. Monitoring patients for the first 2-3 weeks is important. In addition to lenalidomide, the efficacy of an aromatase inhibitor or granulocyte colony-stimulating factor should be evaluated.

Our case report findings suggest that ongoing trials of lenalidomide for cytopenias should consider evaluating the risks and benefits of targeting leukocytoclastic or small vessel vasculitis as a potential new indication for lenalidomide. At present, lenalidomide has no established role in the treatment for ICUS and may actually exacerbate abnormal angiogenesis. However, our case experience demonstrates that lenalidomide should be considered a novel therapeutic agent for ICUS.

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Conflict of Interest

No conflicts of interest were declared by the authors.

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Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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