The impact of COVID-19 in the management of AL amyloidosis and Immunoglobulin Deposition Disease: A single-center experience

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Abstract

Introduction: Patients with AL amyloidosis and immunoglobulin deposition diseases (IDD) are vulnerable during the COVID-19 pandemic due to the immune compromise from the plasma cell disorder and therapy-related immune defects. We describe a local experience in providing care for patients with AL amyloidosis and IDD.

Method: Patient treatment and disease status since the beginning of the pandemic on March 11, 2020, as declared by WHO, were collected and analyzed.

Results: Ninety-six patients with AL amyloidosis and IDD were included. Four patients with IDD and 22 patients with systemic AL amyloidosis were receiving treatment during the pandemic. Since the pandemic, patients’ treatments were discontinued if they achieved VGPR or better postinduction. Seven patients discontinued all treatment after achieving VGPR, and others required treatment modifications. 28 patients have been tested for COVID-19, and all tests have been negative. Three patients died since the pandemic, two from organ complications of systemic AL amyloidosis and one from an unrelated cause.

Conclusion: The management of AL amyloidosis and IDD must be individualized on the clinical characteristics, centers’ access to care under the pandemic restrictions, and the epidemiological aspects of the outbreak.

Keywords

AL amyloidosis, COVID-19, immunoglobulin deposition disease, plasma cell disorder

1 | INTRODUCTION

The outbreak of the novel coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has emerged as a significant challenge for the healthcare system worldwide. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic. Globally, as of November 3, 2020, there have been 46,591,622 confirmed cases of COVID-19, including 1,201,200 deaths, reported to the WHO.1 COVID-19 is a serious health threat and risk varies among the different regions of the world. According to the National Microbiology Laboratory of the government of Canada, 9,597,564 patients have been tested in Canada for COVID-19 as of November 3, 2020.2 From those, 240,263 cases have been reported as positive. In the province of Alberta, 27,664 cases have been confirmed positive for COVID-19 out of a total population of around 4.37 million.3,4
The COVID-19 pandemic poses unprecedented challenges for patients, clinicians, and healthcare systems. Patients with AL amyloidosis and related disorders such as light chain deposition disease and heavy chain deposition disease (LCDD and HCDD), also known and immunoglobulin deposition disease (IDD), are at a high risk of complications associated with COVID-19, in part due to an increased risk for infections, frailty status, advanced age, comorbidities, and immunosuppression. In addition, the therapies used for the management of COVID-19 can be associated with cardiovascular adverse events which are of particular importance for those patients with AL amyloidosis and IDD who have cardiac involvement. Furthermore, immunotherapies and immunoparesis associated with AL amyloidosis could potentially increase the risk of more severe forms of COVID-19.

Currently, most of the recommendations for the management of plasma cell disorders in the era of COVID-19 are not evidence based and thus, it is important to report the experiences of centers to raise awareness of the possible complications and for better understanding of the implications of the pandemic on the treatment of patients with AL amyloidosis and IDD. In the present study, we aimed to assess the impact of the COVID-19 pandemic on the management of patients with AL amyloidosis and IDD at a plasma cell disorders referral center.

2 | METHODS

All consecutive patients with AL amyloidosis and IDD seen at our institution from 2013 to 2020 and registered in the local Plasma Cell Disorders Database were evaluated. Patient treatment and disease status since the beginning of the pandemic on March 11, 2020, as declared by WHO, were collected and analyzed. Patients were treated and followed according to our institutional guidelines. This project has been approved by the Health Research Ethics Board.

2.1 | Statistics

Two-sided Fisher exact test was used to test for differences between categorical variables. Two-sided Fisher exact test was used to test for differences between categorical variables. A P value of <.05 was considered significant. Survival curves were constructed according to the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed by using the SPSS 24.0 software.

3 | RESULTS

Ninety-six patients were registered in the local Amyloid and IDD database. Clinical characteristics are shown in Table 1. Patients with systemic AL amyloidosis were more likely to have lambda restriction as compared to patients with IDD (73% vs 15%, $P = .01$). Serum creatinine level and the percentage of bone marrow plasma cells trended higher in the IDD group compared to systemic AL amyloidosis group, as 50% of cases with LCDD were associated with symptomatic multiple myeloma (MM), but the differences were not significant ($P = .42$ and $P = .39$, respectively).

Among the 15 patient cases with localized amyloidosis, 5 of them had amyloid localized to the lungs, 2 affecting the breast, 2 with eyelid involvement, 1 with vocal cord, 1 with orbital disease, 1 with nodal, 1 with skin, 1 with gastrointestinal, and 1 with genitourinary involvement. None of these patients have progressed or required systemic therapy at the time of analysis.

All patients with IDD presented with renal involvement, and two of the five LCDD patients also developed heart involvement. Finally, one patient with LCDD had gastrointestinal involvement at the time of diagnosis.

3.1 | Current therapies

At the time of analysis, all patients with IDD, localized amyloidosis, as well as 45 out of the 74 patients with systemic AL amyloidosis are alive. Among the 45 cases with systemic AL amyloidosis, 21 are followed with active surveillance and 22 are receiving therapy at our institution (Table 2). The remaining two of the 45 patients have moved to different cities. One patient with HCDD and three patients with LCDD are receiving active therapy.

**Novelty Statement**

1. **What is the NEW aspect of your work?**

We describe our local experience of managing AL amyloidosis and immunoglobulin deposition disease (IDD) during the COVID-19 pandemic.

2. **What is the CENTRAL finding of your work?**

We emphasize that the management of AL amyloidosis and IDD must be individualized based on the biological aspects of the disease, clinical characteristics, centers’ access to care under the current pandemic restrictions, as well as the epidemiological aspects of the outbreak in a particular region.

3. **What is (or could be) the SPECIFIC clinical relevance of your work?**

Currently, most of the recommendations for the management of plasma cell disorders in the era of COVID-19 are not evidence based, and thus, it is important to report the experiences of centers to raise awareness of the possible complications and for better understanding of the implications of the pandemic on the treatment of patients with AL amyloidosis and IDD.
Prior to the pandemic, the local standard care for patients with AL amyloidosis involved four to six cycles of induction therapy with cyclophosphamide, bortezomib, and dexamethasone (CyBord) to achieve very good partial response (VGPR) or greater. A proportion of patients received an alternative regimen including cyclophosphamide, bortezomib, and methylprednisolone (CyBorMe). For patients in VGPR after induction therapy, continuous therapy with bortezomib administered every 2 weeks was decided based on individual features associated with the disease (ie, AL amyloidosis with >10% bone marrow plasma cells and lack of organ response). If complete response (CR) was achieved, patients underwent minimal residual disease (MRD) testing by multiparameter flow cytometry as previously described. MRD was not used to modify therapy but rather to characterize depth of response. Once CR was achieved postinduction, the decision to continue treatment versus discontinuing therapy was made on a case by case basis. In patients on second line or beyond who received lenalidomide, the need for continuous therapy after six cycles was individualized based on hematological response, organ response, and tolerability. Similarly, for patients receiving daratumumab-based regimens, the minimum duration of therapy was 2 years, with a goal of therapy of sustaining CR.

Since the pandemic, patients’ treatments were discontinued if they achieved VGPR or better. Seven patients were receiving daratumumab-based treatment regimens at the time of the pandemic (Table 2). One patient achieved VGPR after seven cycles of daratumumab, lenalidomide, and dexamethasone (DRd) and discontinued treatment modifications

### 3.2 Treatment modifications

Prior to the pandemic, the local standard care for patients with AL amyloidosis involved four to six cycles of induction therapy with...
treatment at the beginning of the pandemic. In the remaining six patients, all patients were allocated to the accelerated program where the drug was infused in 90 minutes, and they were clinically assessed in the chemo-daycare treatment unit to avoid visits to the regular clinic appointments. Two out of the six patients are currently receiving monthly daratumumab infusions, and four patients are receiving twice monthly daratumumab infusions.

Of the five AL amyloidosis patients receiving DRd treatment (Table 2), one patient discontinued DRd therapy after achieving VGPR. Three of the remaining four patients discontinued lenalidomide and instead continue only on daratumumab and dexamethasone. Reasons for lenalidomide discontinuation included grade 3 neutropenia in one patient, grade 2 fatigue in another patient who was in stable remission, and the last patient discontinued lenalidomide after achieving VGPR after six cycles.

Ten patients recently diagnosed with AL amyloidosis since the fall of 2019 were treated with cyclophosphamide, bortezomib, and methylprednisolone (CyBorMe). Methylprednisolone was given at 500 mg IV every 7 days for 3 out of 4 weeks. Four of these patients had been initiated on treatment prior to the pandemic declaration, and six have started treatment since the pandemic began. Two patients required omissions or reductions of methylprednisolone. At the time of this analysis, the four patients who started treatment prior to the pandemic have all achieved CR after five to six cycles of CyBorMe and discontinued treatment. Since the start of the pandemic, six patients with newly diagnosed AL amyloidosis were initiated on CyBorMe and remain on treatment. Four of these six patients had screening for COVID-19 before chemotherapy initiation. All patients not on active treatment were assessed via phone follow-ups, and laboratory testing was delayed at the peak of the outbreak.

3.3 | Telemedicine and diagnostic investigations

As of March 11, 2020, when WHO declared the pandemic, the cancer center initiated a telemedicine program. All patients were contacted by phone and laboratory testing was restricted to local laboratory facilities where the immunocompromised patients were offered reserved spots by the Alberta Health Services. The amyloidosis clinic is run weekly at our institution, and ~90% of the patients were assessed through telemedicine. New cases were seen in the clinic for initial assessments, and investigations and diagnostic imaging studies were done according to prioritization. All patients not on active treatment were assessed via phone follow-ups, and laboratory testing was delayed at the peak of the outbreak.

3.4 | 6-minute walk testing

Patients with AL amyloidosis with heart involvement are assessed monthly at our clinics with a 6-minute walk test (6MWT). At the time of the pandemic declaration, all 6MWT were canceled in the clinics, and instead, patients were instructed to self-monitor their ability to walk and perform activities of daily living.

3.5 | COVID-19 testing

The province of Alberta has one of the highest testing rates in the world (as of November 3, 2020, there were 1,789,173 tests completed for a total population of approximately 4.37 million). COVID-19 testing was performed according to the Alberta Health Services guidelines and was conducted through nucleic acid testing using primers targeting the E (envelope protein) gene of SARS-CoV-2.
At our center, 28 of the 96 patients with AL amyloidosis and IDD have been tested for COVID-19, and all tests have been reported as negative. Six patients with a new diagnosis of AL amyloidosis required therapy initiation after the pandemic was declared. Four out of these six patients underwent screening for COVID-19 prior to therapy start with CyBorMe. So far, 12 out of 22 patients with systemic AL amyloidosis who were on active therapy at any time during the pandemic have been tested. All of these patients were tested due to upper respiratory symptoms. Currently, COVID-19 testing in Alberta is available to any person who wants to be tested regardless of whether symptoms are present or not. Locally, testing for AL amyloidosis or IDD patients is not standardized. Patients do not routinely undergo testing while they are receiving active therapy.

3.6 | Survival outcomes

At the time of analysis, 67 of the 96 patients are alive. Since the pandemic, three patients have died. Two patients diagnosed with systemic AL amyloidosis in 2019 had both discontinued therapy prior to pandemic onset in March 11, 2020. One of them died of amyloid-related cardiac complication, and the other died of an unrelated cause. The third patient’s death was related to an acute gastric complication from a new diagnosis of AL amyloidosis involving the gastrointestinal tract.

The majority of the patients at our institution were diagnosed in the recent past few years (71 of the 96 patients were diagnosed since 2015). The estimated survival curves in Figure 1 for each patient group followed at the Tom Baker Cancer Center (systemic AL amyloidosis, localized AL amyloidosis, IDD patients) show that the majority of the patients were censored early on due to their short follow-up period. The median survival of the systemic AL amyloidosis group has not been reached. All seven IDD patients remain in stable remission during the pandemic.

4 | DISCUSSION

Since the onset of the pandemic, there has been a rapid emergence of studies to identify the vulnerable patient population who are at high risk of severe COVID-19. Several reports suggest that cancer patients, particularly those with hematological malignancies, may have more severe forms of COVID-19 with higher case fatality rates. Unlike symptomatic multiple myeloma which is a hematological cancer with clinical burden of disease arising from a large clonal population of abnormal plasma cells, AL amyloidosis and IDD often involve a smaller clone of defective plasma cells in the bone marrow that secrete toxic proteins in the form of light chains and immunoglobulins which deposit into tissues and cause organ damage. Despite the smaller clonal burden, AL amyloidosis and IDD are associated with risks of infections secondary to the plasma cell disorder itself, and the combination of chemotherapies and immunotherapies used for treatment are associated with immune compromise. Other risk factors to consider in this patient population include older age, presence of other medical comorbidities, and the need for frequent contacts with healthcare facilities and laboratories for follow-up.

The incidence of AL amyloidosis is rare (around 1/5th as common as symptomatic myeloma), and the diagnosis is challenging and often delayed. Furthermore, around 25% of the patients present with advanced organ involvement at diagnosis, and systemic AL amyloidosis is progressive with high morbidity and mortality without treatment. The management of patients with AL amyloidosis and IDD is uniquely challenging, even more so during the COVID-19 pandemic, as dedicated large studies to understand the optimal management of this small yet susceptible patient population during the outbreak are unlikely to take place in a timely manner.

The appropriate therapy and clinical follow-up during the pandemic to reduce viral infection risk while maintaining AL amyloidosis and IDD disease control are unknown. A recent report by Kastritis et al provides an overview of the immune suppression associated with plasma cell directed agents and a comprehensive summary of the anticipated COVID-19-related organ complications in AL amyloidosis patients. Given the variance in COVID-19 infection rates and preventative public health measures across the different regions of the world, treatment decisions must consider local infection patterns and individual patient risk. The majority of AL amyloidosis and IDD patients on treatment at our center has had some form of therapy modification including reduction of dexamethasone in nine cases, discontinuation of lenalidomide in four cases, and discontinuation of CyBorMe in four patients who achieved complete remission after five to six cycles. In Alberta, subcutaneous daratumumab is unavailable outside of a clinical trial setting, and therefore, all patients receiving daratumumab were switched to the accelerated 90-minute infusion program.

In our referral center, 28 of the 96 patients with AL amyloidosis and IDD have been tested for COVID-19, and none have tested positive. The local testing criteria, which initially precluded testing individuals without risk factors or symptoms, has recently been updated such that now anyone requesting a test regardless of the presence of symptoms or risk factors can be tested. According to the latest Infectious Diseases Society of America (IDSA) guidelines, it is recommended that COVID-19 testing is performed in immunocompromised asymptomatic patients and in asymptomatic individuals before immunosuppressive treatments. The feasibility of applying this recommendation for all AL amyloidosis and IDD patients, as well as for other oncology patients, requires ongoing discussion and will depend on the local testing capacities.

Currently, the total number of active cases in Alberta has increased to 5,172 from a nadir of 341 back in May 2020. With the expansion of the testing criteria, continued vigilance is required to monitor for cases of both symptomatic and asymptomatic COVID-19 and to prevent ongoing rise in infection rates. Clinicians should also be prepared for the possibility that patients with undiagnosed but symptomatic AL amyloidosis or IDD may have delayed presentations with advanced disease. One patient with monoclonal gammopathy of undetermined significance (MGUS) on clinical surveillance presented with decompensated heart failure and perforated gastrointestinal tract. Duodenal biopsy was consistent with a new diagnosis of AL amyloidosis. This patient
died of complications from the acute presentation. Another patient on active surveillance for smoldering myeloma developed progressive heart failure syndrome and had repeated admissions for heart failure and infectious complications. The patient was eventually diagnosed with AL amyloidosis during the pandemic and has since been started on treatment with CyBorMe. These patients’ cases represent the risk of delays in prompt diagnosis of AL amyloidosis during the pandemic where clinical follow-up is limited by virtual medicine.

Equally important in the care of AL amyloidosis and IDD patients is to address patients’ emotional burdens that can be associated with feelings of vulnerability to illness and isolation that accompanies social distancing measures. All patients should be informed and engaged in the discussion of their individual infection risks and referred for allied health and community supports when possible.

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CONFLICT OF INTEREST
None to declare.

DATA AVAILABILITY STATEMENT
The data are not available due to privacy and ethical restrictions.

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