Tele-consultation in the management of systemic light chain (AL) amyloidosis: the Pavia amyloidosis centre experience

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ABSTRACT

Introduction: light chain (AL) amyloidosis complexity requires specialized laboratories and use of highly sensitive methods for disease monitoring. During COVID-19 outbreak, access to our diagnostic facility was limited and a telemedicine (TM) program was established to maintain patients' management.

Methods: patients were asked to perform specific blood and urine tests at a local laboratory. Biopsy samples were shipped to Pavia for amyloid typing.

Results: in 2020, 369 TM were performed. For 102 (27%) patients, this was the first contact with our center, 73 (71%) of them received a final diagnosis and the specific therapeutic treatment, whereas in 29 (28%) the diagnostic suspicion was not confirmed. A TM was done in 276 (72%) patients previously evaluated, 214 (80%) of them had systemic AL with 99 (46%) receiving chemotherapy [89 (41%) proceeded with therapy, 10 (4%) suspended due to sustained hematologic response]. Seven (3%) started a new treatment due to loss of hematologic response. In all other cases, hematologic response was confirmed, and treatment free interval was prolonged. In 2021, 109 patients previously evaluated in our Center performed TM, of them 54 (50%) had a systemic AL. In 11 (19%) patients ongoing chemotherapy was proceeded and in one case a new therapy was suggested due to disease progression.

Discussion: through this TM based-approach we reached a final diagnosis in 71% of cases and we assessed hematologic and organ response in local laboratories making clinical decisions. Despite being a response to pandemic, this hub and spoke TM model proved effective in a complex disease.

Key words: *telemedicine, amyloidosis, biomarkers*

INTRODUCTION

Amyloidoses are a group of diseases characterized by the deposition of misfolded proteins into the extracellular compartment of tissues leading to progressive organ dysfunction (1). At present, 42 different proteins have been described as amyloidogenic, the most common being immunoglobulin light chain (AL), transthyretin (ATTR) and amyloid A (AA) (2). The type of precursor protein determines the therapeutic approach, therefore it needs to be accurately characterized on tissue biopsy. Amyloid typing requires adequate expertise and techniques, available at referral centers, such as immunohistochemistry (3), immuno-electron microscopy (4), or mass spectrometry (5). Amyloidoses can be either localized, when the amyloid deposition is limited to the site of production (6), or systemic, when amyloidogenic precursors circulate in the bloodstream and deposit in multiple organs (7). One of the most common form of systemic amyloidosis in Western countries is represented by the immunoglobulin light chain (AL) amyloidosis, a complex hematologic disorder in which the amyloidogenic protein is constituted by monoclonal immunoglobulin free light chain (FLC) secreted by a B-cell clone (8). Given its potential for multi-organ involvement, with heart (69%) the kidney (66%) being the most frequent affected organs (9), AL amyloidosis often arises with a variety of symptoms and clinical manifestations that make diagnosis challenging (1). Due to the progressive nature of the organ damage, a timely diagnosis is key to improve patients survival and long-term quality of life (10). Diagnosis, disease staging and treatment

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strategy are guided by biomarkers of clonal and organ involvement. Serum FLC (sFLC) measurement, serum protein electrophoresis, serum and urine immunofixation (IFE) are used to detect the amyloidogenic monoclonal proteins. Serum FLC levels mirror the underlining clonal burden and correlate with disease outcome (11). Three different assays are available to measure sFLC: Freelite (The Binding Site) (12), N-latex (Siemens Healthineers) (13), and Sebia FLC assay (14), which is still under development. Despite all methods have a similar diagnostic accuracy, they cannot be used interchangeably for disease monitoring due to inter-assay variabilities (15). The extent of organ involvement is assessed by sensitive biomarkers of cardiac [N-terminal pro b-type natriuretic peptide (NT-proBNP), b-type natriuretic peptide (BNP), troponins] (16,17), renal [24 hours proteinuria, albuminuria, estimated glomerular filtration rate (eGFR), urinary albumin/creatinine ratio (UACR)] (18,19) and liver (alkaline phosphatase) damage (20), whose variations are used to evaluate organ response to therapy according to accurate models (21,22). Close monitoring of hematologic and organ biomarkers is fundamental not only to evaluate treatment effectiveness, but also to early detect disease relapse (19,21,23). In this context, an integrated approach between the laboratory and the clinic plays a pivotal role for an effective disease management. In 2020, the SARS-CoV-2 pandemic, and the related mobility restrictions, limited the access to health care services making difficult to diagnose and monitor patients with AL amyloidosis. To continue providing high-quality care to our patients, we implemented an integrated tele-health program that is still in use in our clinical practice. In this retrospective study we attempt to evaluate the role of telemedicine (TM) as a care delivery model in systemic AL amyloidosis.

METHODS

We retrospectively analysed data of patients who performed TM consultation at the Amyloidosis Research and Treatment Center of Pavia from March 2020 to December 2021. Data were drawn from the Ethics Committee approved ReAL amyloidosis registry (NCT04839003), all patients gave written informed consent prior to inclusion in ReAL; patients not previously seen at our Center provided a specific informed consent for the use of clinical data in TM. Subsequently, at the first visit in person in Pavia they were asked to sign the ReAL registry informed consent. From March 2020 to April 2020, the activity of our Center was limited because all non-urgent clinical activities were reduced or revoked. In this scenario, all planned in person visits were cancelled and a TM consultation was proposed to all referred patients. When restrictions were eased in May 2020, TM was proposed to patients that underwent at least one time in-person visit or it was used as a screening tool for patients with suspected systemic or localized amyloidosis. Prior to each TM we asked to send us all available clinical reports and patients were invited to perform at local laboratory the following tests: serum protein electrophoresis, serum and urine immunofixation, sFLC measurement, serum creatinine, NT-proBNP (or BNP), high-resolution troponin I (or high-resolution troponin T), alkaline phosphatase, 24h proteinuria, albuminuria. Patients were recommended to utilize laboratories formerly connected with centers that are already part of the Italian Society of Amyloidosis. Hematologic and organ responses were assessed according to the International Society of Amyloidosis criteria (21,23-26). We verified the consistent use of the same sFLC assay for hematologic response assessment. In selected cases, shipment of biopsy specimen to our Centre was requested for amyloid typing by immune-electron microscopy analysis. We adopted a secure platform to provide a safe communication and data sharing between healthcare providers and patients. The telehealth web platform used in this study was integrated into hospital's interface system for outpatient visits. It enables patients and health-care providers to interact through video-conferencing calls and to safely exchange medical reports. The security of patient's personal data as well as health-related information was guaranteed by the adoption of General Data Protection Regulation (GDPR). Health-care practitioners were provided with personal credentials, and they have access to the telehealth platform exclusively through the hospital network connection. On the other side, patients could access to the web platform using specific credentials related to both patient's tax identification number and medical prescription number. The required medical documentation (i.e. laboratory tests, imaging exams,….) were uploaded by patients on the web-based telehealth platform. Once inputted, data were transferred to the hospital server and ready to be examined by the healthcare providers. At the end of the telehealth visit, the medical report was then forwarded to the patient through the telehealth web platform.

Data are presented as median and interquartile range (IQR). Differences between patients evaluated in 2020 and in 2021 were estimated using the chi-square test. Statistical analysis was conducted with MedCalc® Statistical Software version 20.027 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022)

RESULTS

Patients evaluated using TM were distributed throughout the country as shown in Figure 1.

In 2020, a total of 369 patients underwent TM (Figure 2). Baseline patients' characteristics are listed in Table 1. 102 (27%) patients performed TM as first contact with our centre. In 73 (71%) of them a final diagnosis was established: 18 (24%) systemic AL who received treatment indications, 19 (26%) localized-AL, 33 (45%) wild-type transthyretin (ATTR), 2 (3%) reactive AA and 1 (1%) light chain deposition disease (LCDD). In 13 (13%) patients amyloidosis suspicion was not confirmed and 16 (15%) were already followed and treated by other institutions for systemic AL amyloidosis and a second opinion was discussed. 276 (72%) patients previously evaluated at our Centre underwent TM. Of them, 214 (80%) had systemic AL. Hematologic response assessed were as

follow: 159 (70%) very good partial response (VGPR) or better, 30 (14%) partial response (PR), 25 (11%) stable disease (SD). Loss of hematologic response along with organ progression was detected in 7 (3%) patients and a new line of treatment was suggested. A total of 99 (40%) patients were on active treatment at the time of TM: 89 (35%) patients were suggested to proceed with ongoing chemotherapy and 10 (4%) suspended treatment due to sustained profound hematologic response. In all remaining patients, follow-up without specific treatment intervention was established.

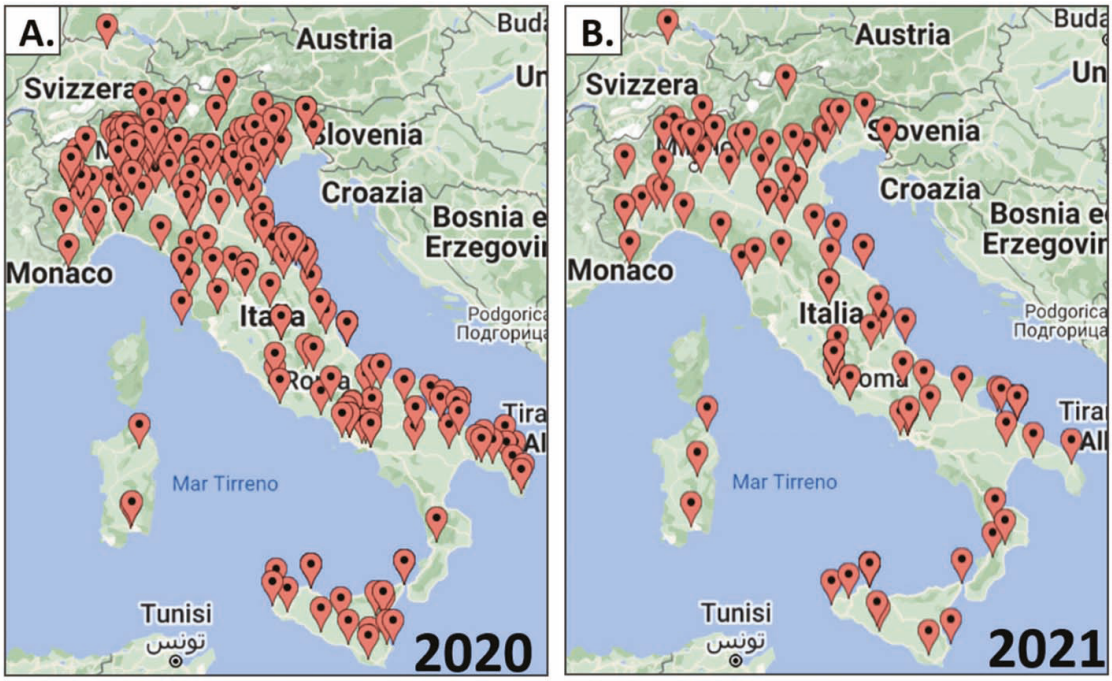

Figure 1
Maps depicting geographic location of patients who underwent telemedicine in 2020 (A) and in 2021 (B).

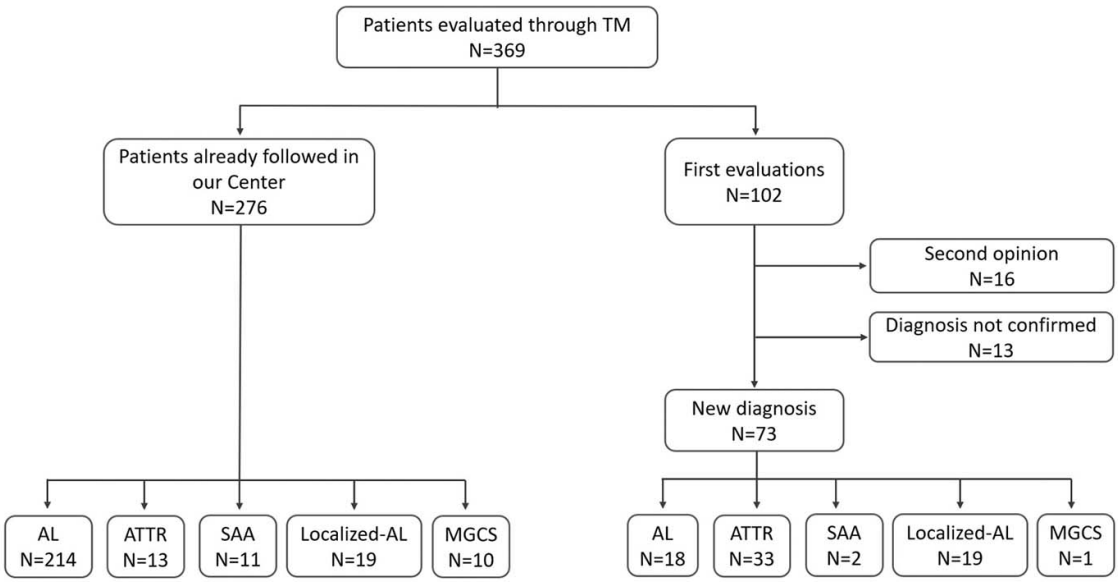

Figure 2
Flow diagram illustrating patients evaluated in 2020 through telemedicine.
AL, immunoglobulin light chain amyloidosis; ATTR, transthyretin amyloidosis; MGCS, monoclonal gammopathies of clinical significance; SAA, serum amyloid A amyloidosis; TM, telemedicine.

In 2021, 109 patients used TM (Table 1): 54 (50%) systemic AL, 44 (38%) localized-AL, 5 (5%) AA, 6 (5%) monoclonal gammopathies of clinical significance. Considering patients affected by AL amyloidosis, 45 (83%) were on Very Good Partial Response (VGPR) or better, 1 (2%) maintained a Partial Response (PR) and 8 (15%) loss their hematologic response. Amongst the latter, a concomitant organ progression was observed in one case and a new line of treatment was suggested; in the remaining cases an in-person visit was subsequently scheduled in our clinic. A total of 11 (20%) patients were on active treatment at the time of TM and all of them proceeded the ongoing therapy. In all remaining cases follow-up was suggested. Moreover, in 2021 a total of 222 patients were screened for AL amyloidosis suspicion on the basis of documentation sent to our Centre. Patients with a high suspicion of AL amyloidosis (n=159) were rapidly scheduled for an in-person visit and in 146 (92%) cases AL amyloidosis diagnosis was confirmed. An increase of 35% in new diagnosis was observed in 2021 compared to 2019. In 2020 a greater number of AL amyloidosis patients were evaluated through TM compared to 2021 (65% *versus* 50%; p 0.003), and a higher percentage of them were on active treatment (40% *versus* 20%; p<0.001). Indeed, in 2021 patients with a sustained hematologic response were mainly proposed to TM [median time and (IQR) from best hematologic response to TM 43 (19-94) *versus* 3 (4-6) months; p<0.001].

DISCUSSION

In this study, telehealth demonstrated to be an effective care delivery system for both diagnosis and management of patients with AL amyloidosis. The introduction of telehealth in our clinical practice guaranteed access to our facilities for patients nationwide (Figure 1). This was of pivotal importance during the pandemic, as the complexity of amyloidosis requires specialized laboratories as well as clinical expertise for disease management. Several studies reported a decrease in new rare disease diagnosis during the pandemic (27). In 2020, Lewis et al. noticed a reduction of 36% in new AL amyloidosis diagnosis (28). This phenomenon has been ascribed to patients limited access to care and to specialized referral centers (29). In our experience, TM allowed us an integrated approach between the laboratory and the clinic, through which we were able to establish new diagnosis in 70% of cases, avoiding diagnostic-delay related to restriction policies. Patients newly diagnosed with AL amyloidosis were stratified according to validated staging system criteria and tailored treatment were suggested. Moreover, in our study TM demonstrated to be also effective for disease monitoring. In patients receiving active chemotherapy both hematologic and organ responses were successfully assessed in local laboratories, and treatment indications were modulated accordingly. Similarly, disease relapses were detected through TM consultations and only in a

Table 1
Patients' characteristics.

	Patients evaluated with TM in 2020 (n=369)	Patients evaluated with TM in 2021 (n=109)	p
Median age, years (IQR)	69 (60-75)	68 (62-76)	0.637
Amyloidosis type, n (%)			
AL	248 (67)	54 (50)	<.001
Localized-AL	38 (10)	44 (38)	<.001
SAA	13 (3)	5 (5)	0.599
ATTR	46 (12)	0 (0)	<.001
Other gammopathies of clinical significance	11 (3)	6 (5)	0.235
Involved organs in AL amyloidosis patients, n (%)			
Heart	136 (55)	33 (61)	<.001
kidney	156 (62)	42 (77)	<.001
Liver	22 (9)	11 (20)	0.706
PNS	17 (7)	3 (5)	0.775
>2 organs	32 (13)	8 (14)	0.693

AL immunoglobulin light chain amyloidosis; ATTR, transthyretin amyloidosis; PNS, peripheral nervous system; SAA, serum amyloid A amyloidosis; TM, telemedicine.

minority of cases (2%) a subsequent in-person visit was required to confirm disease progression. Moreover, TM allowed us to reach remote and most frail patients, who may be unable to travel to our centre, overcoming longstanding barriers. This TM-based approach required a constant information exchange and knowledge sharing between our clinic and local laboratories. This allowed us to build up a network of clinical laboratories nationwide supporting our patient's management that is still in use for patients that are not able to reach our centre. Beyond the SARS-CoV-2 pandemic, TM has been integrated in our clinical practice to follow patients with sustained profound hematologic response undergoing active surveillance or long-term maintenance therapies. Telehealth is emerging as potential tool to speed up diagnosis of several conditions shortening the time from disease onset to the treatment (30-32). In our experience, we observed an increase in new diagnosis following the introduction of TM in our clinical practice. After the pandemic we used TM not only to monitor remote patients but also to screening patients with suspected amyloidosis. As a result, in 2021 an increase of 35% in new diagnosis were observed compared to 2019. Despite being a response to pandemic, this hub and spoke telehealth-based model proved effective in the management of AL amyloidosis.

CONFLICT OF INTEREST

None

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