

# The role of the SARS-COV 2 pandemic on the delay of diagnosis in a case of multiple myeloma associated with AL amyloidosis in HIV-HBV positive patient on antiretroviral treatment.

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## **Abstract:**

*COVID-19 has devastated healthcare systems all over the world and is still raging in Italy. In many countries, patients with chronic illnesses are suffering from delay in diagnostic and treatment management.*

*We report a challenging case of a HIV patient who experienced delay in diagnosis of multiple myeloma due to COVID-19 pandemic restrictions.*

*Global cooperation to ensure equity and responsiveness to local contexts is essential on the difficult path ahead to ending the COVID-19 pandemic, as treatment for one potentially curable disease should not be performed at the expense of another.*

**Keywords:** COVID-19; HIV; COVID-19 and PLWH

## **1. BACKGROUND**

The COVID-19 pandemic has devastated healthcare systems all over the world and it is still raging in Italy, and HIV care, as for many other chronic conditions, has been negatively impacted by it.

Many HIV clinics share staff and logistics with infectious diseases facilities, which are now on the frontline in tackling COVID-19 and are likely to be fully occupied with the current SARS-CoV-2 situation, while the beds for other infectious diseases have been dramatically reduced.<sup>1</sup>

Although Highly Active Antiretroviral Therapy (HAART) has significantly changed the natural history of HIV infections<sup>2</sup> leading to a dramatic reduction of HIV-related morbidity and mortality, Late Presenters (LP) and AIDS presenters still represent a huge challenge for clinicians.<sup>3,4</sup> Long term implications are higher risk of mortality over a longer period, possible increased risk of some non-AIDS events happening, increased risk of cognitive impairment, and increased hospital care/drug costs over 7–8 years.<sup>2,5,6,7</sup>

Light chain type (AL type) amyloidosis is a rare plasma cell dyscrasia related to abnormally folded monoclonal immunoglobulin free light chains deposition in extracellular space of tissues or organs driving to organ failure. Amyloidosis is particularly difficult to diagnose, and some symptoms could mimic other common disorders. The suspicion of AL amyloidosis should arise in patients presenting a non-diabetic nephrotic syndrome, a hypertrophic cardiomyopathy, hepatomegaly, or chronic inflammatory demyelinating polyneuropathy or polyclonal gammopathy associated with fatigue, oedema, weight loss or paraesthesia. It is secondary to multiple myeloma (MM) in 5%-15% of cases and often under-diagnosed due to its polymorphic presentation.<sup>8</sup>

Multiple Myeloma (MM) is a clonal plasma cell proliferative disorder accounting for approximately 10% of hematologic malignancies.<sup>9</sup> MM may manifest with hypercalcemia, renal failure, anaemia, and lytic bone lesions (CRAB symptoms), or may be detected at an asymptomatic stage.<sup>10</sup> MM cells produce high amounts of immunoglobulin light chains, immunoglobulin light and heavy chains, or heavy chain fragments. The 2-year survival for MM is currently 87%, risen over the last decades owing to the introduction of newer therapies.<sup>11</sup> Amyloidosis (AL amyloidosis) is associated with a plasma-cell dyscrasia and amyloidosis-related clinical features may be the earliest manifestations of multiple Myeloma.<sup>12,13</sup>

Here we report a case of a HIV positive patient with a medical history of HBV coinfection and hypertension who experienced a delay in diagnosis of AL amyloidosis associated with multiple myeloma due to COVID-19 pandemic hospital access restrictions.

## 2. CASE PRESENTATION

A 49-year-old male who had had intercourse with men was diagnosed with HIV-1 infection in early 2010, when he was admitted to our Infectious Disease Unit due to Pneumocystis jirovecii pneumonia (PJP) associated with oral candidiasis.

On admission, HIV Viral Load (VL) was 234,686 copies/ml and T CD4+ count was 213 cells/ $\mu$ L. He was also diagnosed with HBV infection (positive HBsAg, HBcAb IgG, HBeAb; negative HBeAg and HBsAb; HBV-DNA was 50.000 IU/ml). Markers of HCV, HAV, Syphilis and Quantiferon test for Latent Tuberculosis Infection were negative.

He was treated with cotrimoxazole and dexamethasone for PJP for 3 weeks and with fluconazole, while antiretroviral therapy was started with lamivudine, tenofovir disoproxil, and lopinavir/ritonavir after genotypic resistance assessment.

After hospital discharge, the patient underwent outpatient follow-up. In 3 months, he reached HIV and HBV VL undetectability and T CD4+ count of 380 cells/ $\mu$ L.

On August 10<sup>th</sup>, 2017, ART was switched to emtricitabine/tenofovir alafenamide plus dolutegravir to reduce pharmacological impact on bones. HIV-VL remains undetectable and T CD4+count was 580 cells/ $\mu$ L.

On September 3<sup>rd</sup>, 2019 laboratory examinations showed a haemoglobin level of 15.5 g/dl, a red blood cell count of  $4.66 \times 10^6/\mu$ l, a white blood cell count of 6,800/ $\mu$ l, a platelet count of 187,000/ $\mu$ l, creatinine levels of 0.87 mg/dl (eGFR by CKD-EPI: 102.1 ml/min). HIV RNA Viral Load (VL) was less than 20 copies/ml and T CD4+ count was 563 cells/ $\mu$ L.

On March 3<sup>rd</sup>, 2020 the patient should have performed laboratory testing but, due to COVID-19 pandemic restrictions, the follow-up was postponed until August 28<sup>th</sup>. On that date, the patient referred to the onset of pollakiuria, nocturia, and oedema of the lower limbs. Blood examinations showed increased creatinine levels of 1.79 mg/dl (eGFR by CKD-EPI: 43.5 ml/min). The following day, new blood examinations revealed a further increase in creatinine

levels (2.35 mg/dl; eGFR by CKD-EPI: 31.3 ml/min) and  $\beta$ 2-microglobulin level of 7.65 mg/l.

Due to renal failure, Tenofovir was removed from ART regimen which was then switched to doravirine plus raltegravir while entecavir 0.5 mg/die was added to treat HBV infection.<sup>14</sup>

On November 30<sup>th</sup>, due to further renal function deterioration (creatinine levels were 5.28 mg/dl, 24-hour-proteinuria was 4,8 g/24h), the patient was admitted to the emergency department where an abdominal CT scan was done, showing paraaortic, interaortocaval and paracavallymphadenomegaly (max diameter 1,3 cm); perihepatic and pelvic fluid collection; pleural and pericardial effusions.

The following day, the patient was transferred to the Nephrology Department to continue the diagnostic assessment. Upon admission, blood tests revealed elevated levels of creatinine (5.7 mg/dl),  $\beta$ 2-microglobulin (17 mg/l), along with anaemia (Hb 9,5 g/dl), and irrelevant inflammatory markers and procalcitonin levels. At the same time, a dialytic treatment was started.

On December 3rd, serum (SIFE) and urine (UIFE) immunofixation electrophoresis were conducted. UIFE but not SIFE showed the presence of monoclonal components (non associated  $\kappa$ -light chain and monoclonal free  $\kappa$ -light chains). Moreover, an echocardiography with color-doppler showed thickened left ventricular walls along with mild decline in left ventricular ejection fraction.

On December 4th, a kidney biopsy showed an amorphous eosinophilic material positive for Congo red stain with characteristic apple-green birefringence in the amyloid deposits involving the glomeruli, vessels, and interstitium. In addition,  $\kappa$ -light chains were detected with direct immunofluorescence method. Due to these findings, diagnosis of AL-Amyloidosis in the patient with suspected multiple myeloma was made.

On December 18th, while waiting for bone marrow biopsy result performed 3 days before, the patient started CyBorD regimen (cyclophosphamide, bortezomib and dexamethasone) omitting cyclophosphamide due to eGFR by CKD-EPI of 6 ml/min. In addition, the patient received antimicrobial and antiviral prophylaxis with acyclovir and cotrimoxazole.

Meanwhile, the patient performed a total body CT scan (negative for focal osteolytic lesions), a colonoscopy (negative), and an upper endoscopy (EGD) which showed a *Helicobacter pylori* mild chronic gastritis.

Finally, on January 4th, 2021 after the bone marrow smear showed that the proportion of plasma cells with  $\kappa$ -light chain restriction was 23%, the patient was diagnosed with micromolecular multiple myeloma associated with amyloidosis. On the same day, the patient was discharged with the decision of continuing antineoplastic therapy according to VTD protocol (bortezomib, thalidomide, and dexamethasone) and a three times/week dialysis program.

### 3. DISCUSSION AND CONCLUSIONS

The pressure on healthcare systems due to the COVID-19 pandemic has had a huge impact on new diagnoses, the follow up and the overall survival rates of patients affected by malignancies. The overall number of new diagnoses steadily decreased in northern and central Italy during the lockdown due to the COVID-19 pandemic (weeks 11-20 of 2020) as it was lower (-44.9%) when compared to the same period of 2018-2019.<sup>15</sup>

TDF is a nucleotide reverse transcriptase inhibitor that is a first-line treatment of HIV.<sup>16</sup> Chronic exposure to TDF has been associated with 34% increased risk of proteinuria, 11% increased risk of rapid decline, and 33% increased risk of chronic kidney disease. Switching from a TDF-containing to a TAF-containing regimen is justified as the latter was non-inferior for maintenance of viral suppression and led to improved bone mineral density and renal function.<sup>17</sup> TAF has so far been approved for clinical use in combination with emtricitabine.

TAF/Emtricitabine should be discontinued in patients with estimated CrCl that declines below 30 mL/min during treatment.<sup>18</sup>

Plasma cell disorders (included MM) occur at an increased frequency in HIV-infected patients. Two main mechanisms probably contribute to the development of plasma cell disorders in this population of patients: antigenic stimulation and immunodeficiency.<sup>19</sup> An epidemiological study conducted by Dal Maso et al. has shown a 2-to-5-fold increase in the risk of developing MM in HIV-infected patients.<sup>20,21</sup> In the general population, MM is a disease that mainly affects the older patients (median age of patients at diagnosis is approximately 66-70 years).<sup>22</sup> HIV-positive patients presented MM at a significantly younger age, along with fewer osteolytic lesions, less renal impairment, and lower neutrophil counts.<sup>23</sup>

The interval between HIV infection and the diagnosis of MM remains to be determined. In some reported cases, MM was the first manifestation of HIV/AIDS infection.<sup>24,25</sup> In our case, the diagnosis of MM occurred approximately ten years after diagnosis of HIV infection.

In half of patients with multiple myeloma, the end stage renal disease is a complication encountered in evolution, while approximately 20–30% of patients present renal impairment since the diagnosis.<sup>26</sup>

As far as we know, there is no a direct link between HIV infection and the development of AL amyloidosis<sup>27</sup> and only few cases of amyloidosis have been reported in HIV positive patients.<sup>28</sup> The number of new patients diagnosed as having AL amyloidosis is much lower than the actual number of new cases of multiple myeloma<sup>29</sup>, but it represents the most common type of systemic amyloidosis in western countries.<sup>30</sup> The occurrence of AL amyloidosis in patients with symptomatic MM or other B-cell lymphoproliferative disorders is unusual.<sup>30</sup> Kidney involvement is the most frequent complication, as it is found in two thirds of patients at the time of diagnosis, and it is characterized by heavy proteinuria, nephrotic syndrome, and impaired renal function in half of the patients.

The goal of the treatment is to reduce the availability of the precursor protein, using chemotherapy to target the plasma cell clone producing the amyloid light chains. All treatment strategies which have shown efficiency in multiple myeloma or in lymphoproliferative disorders can be used.<sup>30</sup>

Chemotherapy regimens for MM in HIV-infected patients are the same as those for HIV-negative MM patients, and usually consist of 2 to 3 drug combinations of thalidomide, lenalidomide, bortezomib, and dexamethasone.<sup>19</sup>

The reported case highlights the impact of the COVID-19 pandemic on the care of both acute and chronic medical conditions unrelated to COVID-19. HIV patient care has been critically hit by the pandemic, especially in terms of diagnostic delay of non-AIDS conditions. There are many other patients who have suffered or will suffer serious consequences due to delays in diagnosis and treatment. As the SARS-CoV-2 pandemic continues, to provide continuity to medical care is of paramount importance, especially in frail patients like PLWH.

This pandemic is a reminder, also for high-income countries, that infectious diseases can have a tremendous impact on economies and lives, and a rapid development and implementation of effective vaccines against these diseases should remain a global priority. Global cooperation is essential to ensure equity and responsiveness to local contexts on the difficult path ahead to ending the COVID-19 pandemic. Finally, and again, it cannot be accepted that treatment for a potentially curable disease is performed at the expense of another one.

## **Declarations**

### ***Ethics approval and consent to participate***

Not applicable

### ***Consent to publish***

Written informed consent for publication of clinical details was obtained from the patient and it is contained in the patient's clinical record.

### ***Availability of data and materials***

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. We used only information contained in the patient's clinical record.

### ***Competing interests***

The authors declare that they have no competing interests

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### ***Authors' contributions***

- I. EC wrote the paper;
- II. AM, SU, MI, CE, GU, AC, FC, VM and BMC gave clinical assistance to the case;
- III. FC and VM searched literature references;
- IV. MC BC and BMC revised the paper.

### **All authors read and approved the final manuscript**

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### **REFERENCES:**

1. Kowalska, J. D. *et al.* HIV care in times of the COVID-19 crisis — Where are we now in Central and Eastern Europe? *Int. J. Infect. Dis.* **96**, 311–314 (2020).
2. B.M. Celesia, D. Castronuovo, M.R. Pinzone, F. Bellissimo, M.T. Mughini, G. Lupo, M.R. Scarpino, M. Gussio, F. Palermo, S. Cosentino, B. Cacopardo, G. Nunnari *Late presentation of HIV infection: predictors of delayed diagnosis and survival in Eastern Sicily*
3. Marino, A. *et al.* Rapid emergence of cryptococcal fungemia, Mycobacterium chelonae vertebral osteomyelitis and gastro intestinal stromal tumor in a young HIV late presenter: A case report. *BMC Infect. Dis.* **18**, (2018).
4. Celesia, B. M. *et al.* Successful extracorporeal membrane oxygenation treatment in an acquired immune deficiency syndrome (AIDS) patient with acute respiratory distress syndrome (ARDS) complicating pneumocystis jirovecii pneumonia: A challenging case. *Am. J. Case Rep.* **21**, (2020).
5. Antinori, A. *et al.* Late presentation of HIV infection: A consensus definition. *HIV Med.* **12**, 61–64 (2011).
6. Celesia, B. M. *et al.* Is it Safe and Cost Saving to Defer the CD4+ Cell Count Monitoring in Stable Patients on Art with More than 350 or 500 cells/ $\mu$ l? *Mediterr. J. Hematol. Infect. Dis.* **11**, e2019063 (2019).
7. Scherzer, R. *et al.* Association of tenofovir exposure with kidney disease risk in HIV infection. *Aids* **26**, 867–875 (2012).
8. Randrianarisoa, R. M. F. *et al.* Light chain Amyloidosis (AL) associated with multiple myeloma revealed by peripheral bilateral polyarthritis: a case report. *Clin. Case*

- Reports***9**, 2153 (2021).
9. Dimopoulos, M. A. *et al.* Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann. Oncol.***32**, 309–322 (2021).
  10. Nakaya, A. *et al.* Impact of CRAB symptoms in survival of patients with symptomatic myeloma in novel agent era. *Hematol. Rep.***9**, 16–18 (2017).
  11. Fonseca, R. *et al.* Trends in overall survival and costs of multiple myeloma, 2000-2014. *Leukemia***31**, 1915–1921 (2017).
  12. Gertz, M. A. & Zeldenrust, S. R. Treatment of immunoglobulin light chain amyloidosis. *Curr. Hematol. Malig. Rep.***4**, 91–98 (2009).
  13. Wang, X., Xie, H. & Zhang, L. Multiple myeloma with onset of pancreas involvement. *Med. (United States)***98**, 1–5 (2019).
  14. Marino, A. *et al.* Entecavir resistance in a patient with treatment-naïve HBV: A case report. *Mol. Clin. Oncol.***14**, 113 (2021).
  15. Ferrara, G. *et al.* Cancer diagnostic delay in northern and central Italy during the 2020 lockdown due to the coronavirus disease 2019 pandemic: Assessment of the magnitude of the problem and proposals for corrective actions. *Am. J. Clin. Pathol.***155**, 64–68 (2021).
  16. Babb, B. A. & Pruet, M. K. EACS Guidelines 2020. **58**, 867–869 (2020).
  17. De Clercq, E. Tenofovir alafenamide (TAF) as the successor of tenofovir disoproxil fumarate (TDF). *Biochem. Pharmacol.***119**, 1–7 (2016).
  18. European Medicines Agency. [https://www.ema.europa.eu/en/documents/product-information/descovy-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/descovy-epar-product-information_en.pdf). doi:10.2307/j.ctvdf0dxq.12.
  19. Coker, W. J., Jeter, A., Schade, H. & Kang, Y. Plasma cell disorders in HIV-infected patients: Epidemiology and molecular mechanisms. *Biomark. Res.***1**, 1–12 (2013).
  20. Maso, L. D. & Franceschi, S. HIV-related haemolymphopoietic neoplasms. *LANCET Oncol. Lancet Oncol***4**, 110–19 (2003).
  21. Ceccarelli, M. *et al.* Non-AIDS defining cancers: A comprehensive update on diagnosis and management. *European Review for Medical and Pharmacological Sciences* vol. 24 3849–3875 (2020).
  22. Kazandjian, D. Multiple myeloma epidemiology and survival: A unique malignancy. *Semin. Oncol.***43**, 676–681 (2016).
  23. De Groot, J. J. B., Webb, M. J., Raubenheimer, J. E., Struwig, M. C. & Louw, V. J. Concomitant HIV infection in newly diagnosed multiple myeloma patients is hard to recognise and should be tested for routinely in areas of high endemicity. *South African Med. J.***107**, 781–787 (2017).
  24. Pouli, A. *et al.* Multiple myeloma as the first manifestation of acquired immunodeficiency syndrome: A case report and review of the literature. *Ann. Hematol.***80**, 557–560 (2001).
  25. Facciola, A. *et al.* Malignant melanoma in HIV: Epidemiology, pathogenesis, and management. *Dermatologic Therapy* vol. 33 (2020).
  26. Desport1, E. *et al.* AL Amyloidosis - Review. *Rom. J. Morphol. Embryol.***54**, 187–190 (2013).
  27. Denman, J., Manavi, K. & Cook, M. Lenalidomide as a treatment for relapsed AL amyloidosis in an HIV-positive patient. *Int. J. STD AIDS***28**, 1045–1047 (2017).
  28. Chan-Tack, K. M. *et al.* Acute renal failure and nephrotic range proteinuria due to amyloidosis in an HIV-infected patient. *Am. J. Med. Sci.***332**, 364–367 (2006).
  29. Kyle, R. A. *et al.* Incidence of AL Amyloidosis in Olmsted County, Minnesota, 1990 through 2015. *Mayo Clin. Proc.***94**, 465–471 (2019).
  30. Desport1, E. *et al.* AL Amyloidosis. *N. Engl. J. Med.***349**, 583–596 (2003).