CASE REPORT

A multidisciplinary case report of multiple myeloma with renal and cardiac involvement: a look beyond amyloidosis

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Abstract

Background: Multiple myeloma (MM) is a malignant neoplasm associated with kidney involvement in nearly half of the patients. Cast nephropathy, monoclonal immunoglobulin deposition disease (MIDD), and light chain (AL) amyloidosis are the most common monoclonal immunoglobulin-mediated causes of renal injury. Cardiac involvement is also present in MM, characterized by restrictive cardiomyopathy generated by light chain deposit or amyloid. Thromboembolic complications such as deep vein thrombosis or pulmonary embolism are also described.

Case presentation: We present an unusual multidisciplinary case of a woman with a newly diagnosed MM associated with severe proteinuria and high natriuretic peptide. A renal and fat pad biopsy with Congo red staining was performed but amyloid deposition was not discovered. While immunofluorescence on fresh frozen unfixed tissue was not contributory, the immunofluorescence on fixed tissue and electron microscopy revealed the correct diagnosis. During subsequent investigations, two intracardiac right-sided masses and massive pulmonary embolism were also detected.

Conclusions: This case highlights that multiple organ involvement in patients with MM may result from a combination of paraprotein-dependent and -independent factors. Moreover, renal diseases induced by monoclonal gammapathies are a group of complex and heterogeneous disorders. Their subtle presentation and their potential multiorgan involvement require the expertise of a multidisciplinary team able to provide the most appropriate diagnostic and therapeutic assessment.

Keywords: Multiple myeloma, Amyloidosis, Light-chain deposition disease, Renal vein thrombosis, Intracardiac thrombi

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Table 1  Cardiac complications in multiple myeloma

| Cardiac complications in multiple myeloma | Chemotherapeutic treatment related: |
|------------------------------------------|-----------------------------------|
| Amyloid or light chain deposition related |                                    |
| Restrictive cardiomyopathy              | Ischemic heart disease             |
| Pericardial effusion                    | Congestive heart failure           |
| Pericarditis                            | Pulmonary hypertension             |
| Cardiac dysfunction                     | Cardiac dysfunction (irreversibly and dose-related or dose-independent) |
| Thromboembolism                         | Thromboembolism                     |
| Arrhythmia (atrial fibrillation)        | Arrhythmia                         |
| Intramiocardial massess                 |                                    |
### Table 2: Patient's laboratory values

|                               | Normal range | Onset | Month 1 | Admission (mo 2) | After surgery | After 1 month of CHT (mo 4) | After 3 months of CHT (mo 6) | After 6 months of CHT (mo 9) | 1mo after ASCT (mo 11) |
|-------------------------------|--------------|-------|---------|------------------|---------------|----------------------------|------------------------------|-------------------------------|-------------------------|
| **Serum creatinine (mg/dl)**  | 0.50–1.10    | 1.5   | 19      | 2.36             | 1.99          | 1.31                       | 1.34                         | 1.33                         | 1.28                    |
| **eGFR (CKD-EPI) (ml/min/1.73m²)** | 90–140     | 40    | 298     | 22.9             | 28.2          | 46.7                       | 46.4                         | 46                           | 48                      |
| **urea (mg/dl)**              | 10–50        | N/A   | 80      | 80               | 80            | 110                        | N/A                          | 50                           | 50                      |
| **Hb (g/dl)**                 | 12–16        | 13.2  | 12.1    | 13               | 10.3          | 11                         | 10.7                         | 12.3                         | 10.5                    |
| **WBC (10⁹/L)**               | 40–100       | 8.10  | 72.4    | 95.5             | 12.70         | 560                        | 995                          | 503                          | 325                     |
| **PLT (10⁹/L)**               | 140–440      | 168   | 127     | 70               | 131           | 117                        | 171                          | 21                           |                         |
| **INR**                       | 0.8–12       | N/A   | N/A     | N/A              | 2.7           | 2.1                        | 2.6                          | 3.0                          | 2.5                     |
| **aPTT (sec)**                | 25.0–38.0    | N/A   | N/A     | N/A              | 25.9          | 31                         | N/A                          | 46.1                         | N/A                     |
| **Serum immunofixation**      | Negative     | N/A   | Kappa FLC | Kappa FLC      | Kappa FLC     | Kappa FLC                  | Kappa FLC                    | Neg                          | Neg                     |
| **Kappa light-chain (mg/L)**  | 3.30–19.40   | N/A   | 96000   | 93304            | 96256         | 364                        | 17.5                         | 18.76                        | 0.75                    |
| **Lambda light-chain (mg/L)** | 5.7–26.30    | N/A   | 533     | 464             | 5.46          | 21.62                      | 11.98                        | 114                          | 1.11                    |
| **FLC ratio**                 | 0.26–1.65    | N/A   | 18000   | 21277            | 17629         | 167                        | 1.46                         | 1.64                         | 0.68                    |
| **D-Dimer (ng/ml)**           | < 500        | N/A   | N/A     | 7541             | 4796          | N/A                        | N/A                          | 436                          | < 200                   |
| **NT-Pro-BNP (pg/ml)**        | 1–125        | N/A   | 1242    | 722             | N/A           | N/A                        | N/A                          | 1.566                        | N/A                     |
| **Troponin T HS (pg/ml)**     | < 14         | N/A   | N/A     | 328             | 2298          | N/A                        | N/A                          | 288                          | N/A                     |
| **Bence-Jones proteinuria (g/24 h)** | Negative     | N/A   | 1.71    | 0.65             | 1.61          | Trace                      | Neg                          | Neg                          | Neg                     |
| **Proteinuria (g/24 h)**      | < 0.15       | 70    | 65.8    | 28              | N/A           | 12                         | 3.15                         | 1.07                         | 1.1                     |
| **β₂-microglobulin (mg/L)**   | 1.2–2.5      | 102   | 133     | 146             | 133           | 58                         | 4                            | N/A                          | N/A                     |
| **IL-6 (pg/ml)**              | 0.00–100     | N/A   | N/A     | N/A             | 1135          | 74.2                       | 24                           | N/A                          | N/A                     |
| **Albumin (g/L)**             | 35–50        | N/A   | 40      | 35.6            | 40            | 27                         | 36.5                         | 45.9                         | 40.0                    |
| **Total serum protein (g/dL)**| 60–82        | N/A   | N/A     | 76              | 4.5           | 5                          | 5.3                          | 6.1                          | 5.8                     |
| **Total serum calcium (mg/dl)**| 86–102      | 93    | N/A     | 99              | 8.8           | 76                         | 9.2                          | 96                           | 83                      |
| **IgG (g/L)**                 | 70–160       | N/A   | N/A     | 0.91             | 1.15          | 2.67                       | 2.15                         | 3.91                         | 3.09                    |
| **IgA (g/L)**                 | 0.7–4.00     | N/A   | N/A     | < 0.07          | 0.09          | 0.56                       | 0.55                         | 0.61                         | < 0.07                  |
| **IgM (g/L)**                 | 0.4–2.30     | N/A   | N/A     | < 0.04          | 0.05          | 0.71                       | 0.16                         | 0.23                         | 0.11                    |
| **Gamma-globulin (%)**        | 11.1–18.8    | N/A   | N/A     | 22.2            | 19.7          | 5.3                        | 3.8                          | 6.2                          | 6.7                     |
| **C3 (g/L)**                  | 0.90–1.80    | N/A   | N/A     | 13              | N/A           | 5.3                        | N/A                          | 1.12                         | N/A                     |
| **C4 (g/L)**                  | 0.10–0.40    | N/A   | N/A     | 10              | N/A           | 0.32                       | N/A                          | N/A                          | N/A                     |

*ASCT autologous stem cell transplantation, CHT chemotherapy, mo month, eGFR estimated Glomerular Filtration Ratio, FLC Free light chain, Hb Hemoglobin, IL-6 Interleukin 6; INR, International Standardized Ratio, N/A not available, Neg negative, PLT platelet, WBC white blood cell*
showed segmentary “ground pepper-like” deposits in
the subendothelial space and the glomerular basement
membranes (GBM). Similar deposits were observed
along the tubular basement membrane (TBM). Extensive
podocyte foot process effacement was seen with
no sub-epithelial or mesangial electron-dense deposits
(Fig. 3E). The final diagnosis was “kappa light chain
deposition disease (LCDD)”.

The patient fully recovered from surgery. A new TTE
showed preserved function of both ventricles (EF 58%,
TAPSE 20 mm, RV-RA gradient 25 mmHg) or major val-
vular disease. No new intracardiac masses were detected
(video, Additional file 1).

A 3-months follow-up CT showed the persistence of
only a partially calcified thrombus in the right pulmonary
artery’s distal branches, warfarin was continued.
After 4 cycles of VTD protocol (Bortezomib, Thalidomide, Dexamethasone), the patient presented a very-good partial hematologic remission. Afterwards, she received autologous hematopoietic stem cell transplantation, with a stable complete hematologic remission and a progressive improvement of proteinuria and renal function (Table 2).

**Discussion and conclusions**

This case proves that a step-by-step diagnostic flow chart and a multidisciplinary clinical evaluation are crucial to obtain the right diagnosis.

At the time of admission, the worsening of renal function with nephrotic-range proteinuria, elevated kappa FLC, increase NT-proBNP and hs-cTnT strongly suggested AL systemic amyloidosis with both renal and cardiac involvement. However, Congo red staining negativity of two biopsies, made a mandatory reassessment of differential diagnosis for cardiac and renal involvement.

Nephrotic range proteinuria without the full-blown nephrotic syndrome could suggest secondary/maladaptive focal segmental glomerulosclerosis, in particular when one or more risk factors are present, such as for obesity and reduced renal parenchymal mass [3], as observed in our patient. Moreover, the left renal vein
thrombosis, observed on CT, could have explained at least in part the degree of proteinuria [4].

In the context of monoclonal gammopathies of renal significance, not all patients with high levels of paraprotein present with reduced renal function, although FLC levels > 800 mg/L are good predictors of severe renal failure [5]. However, despite the extremely high levels of kappa FLC, our patient showed only a mild-to-moderate worsening of kidney function and no histological signs of cast nephropathy. In fact, physico-chemical properties of the secreted paraprotein may determine pathological features, for which a variety of Ig-dependent and -independent mechanisms have been described [6].

Among patients with monoclonal gammopathies, those presenting with heavy proteinuria and milder renal impairment are more likely to have AL amyloidosis, LCDD or HCDD [7]. Excluding the first, patients with LCDD usually present with proteinuria (nephrotic-range proteinuria is seen in about 50% of cases), microscopic hematuria, hypertension, and variable degrees of renal insufficiency. Clinical presentation depends on several histopathological aspects: the site of the FLC deposition in renal compartments, the extent of chronic lesions, the degree of foot process effacement, and overlap with myeloma cast nephropathy [2].

The IF is essential for the definitive diagnosis of LCDD. However, there are rare cases (as in our patient) in which the immune deposits and paraproteins are ‘masked’ on routine IF, resulting in false-negative staining on fresh frozen tissue, and paraffin immunofluorescence can be used to unmask FLC deposits [8]. LCDD diagnosis via kidney biopsy permitted to establish an early and correct chemotherapy regimen that led to a complete hematologic response, which is mandatory to improve renal and global outcomes.

In patients with clinical suspicion of AL amyloidosis or LCDD, increased NT-proBNP and hs-cTnT represent sensitive markers to identify cardiac involvement [9]. Surprisingly, echocardiography showed no signs of cardiac dysfunction [10], in particular no increased wall thickness, or diastolic dysfunction while, it demonstrated multiple right-sided cardiac masses. According to the patient’s history and masses aspects, only a few hypotheses were acceptable: heart thrombi [11], mobilized deep venous thrombi, and, less likely, primary or metastatic tumors [12].

In our case, since both right chambers were involved, a metastasis from a primary neoplasm (renal-cell carcinoma or hepatocellular carcinoma) extended through the inferior vena cava to the right side of the heart should be also considered. However, no evidence of renal or hepatic lesions was appreciated on an abdominal CT.

Of note, the right atrium is probably the predominant location of plasmacytoma involving the heart but it is a rare presentation of MM [13].

In our patient, histological examination of the intracardiac masses confirmed the thrombotic nature.

Among different complications of MM a high risk of venous thrombosis has been previously described. The thrombophilic state is multifactorial and often divided in three categories: (i) malignancy-related: is potentially characterized by the hyperviscosity syndrome due to increased paraprotein content, the release of inflammatory cytokines (as IL-6), and several changes in coagulation (as an increased von Willebrand factor or factor VIII) [14]; (ii) patient-related: such as the presence of central venous access devices, hypoalbuminemia, renal failure, immobilization and obesity [15], and (iii) therapy-related: as during treatment with immunomodulatory drugs (thalidomide lenalidomide and pomalidomide) which have a prothrombotic effect. Current literature lacks of data about a possible direct pathogenetic role of paraproteins in venous thrombosis [16]. In some case reports, the monoclonal light chain is identified as an interfering factor in functional assays and coagulation tests causing dysfibrinogenemia [17]. In our case, a lot of contributory factors are involved in the development of the prothrombotic state, such as obesity, very high levels of free light chains and hypoalbuminemia.

Considering the extension of the thrombosis and the plausible chronic state, anticoagulant therapy alone was considered insufficient.

In case of acute pulmonary embolism with hemodynamic instability, thrombolysis is recommended while surgical embolectomy is considered as an alternative in patients not responsive to thrombolytic therapy or with acute hemodynamic deterioration. Surgical thrombectomy removal, instead, is the treatment of choice in chronic thrombosis of the pulmonary tree [18]. In our report, the operability of the patient was approved by a multidisciplinary team after evaluation of several parameters: NYHA class, the risk of rapid hemodynamic deterioration, and the patient’s quaod vitam prognosis. Therefore, surgical thrombectomy was considered the best option. Moreover, the heart surgical intervention was crucial in order to prevent acute RV dysfunction, recurrent pulmonary embolism and thus cardiogenic shock.

The natural history and prognosis of MIDD depend on the severity of renal failure at diagnosis, the presence of an underlying MM, and the delay in the hematologic response to chemotherapy. Additionally, LCDD patients with cardiac involvement have poorer survival and a significantly higher risk of treatment-related mortality after ASCT [19]. Moreover, our patient showed several parameters associated with unfavorable MM
outcome. Some negative prognostic factors are widely accepted, such as high-risk chromosomal abnormalities, high serum β2-microglobulin (≥5.5 mg/L), and low serum albumin [20]. Other prognostic factors are not widely validated, such as immunoparesis, which have a negative impact on the progression-free survival [21], high serum IL-6 levels [22], or extremely high levels of FLC [23], which have been shown to play a prominent role in the development of kidney damage.

Overall, both early diagnosis and prompt treatment with bortezomib and ASCT-based combinations can improve the prognosis of LCDD, by reducing circulating immunoglobulins, preserving renal function, and improving overall survival, even in patients with a severe disease at onset.

In conclusion, in patients with MM, multiple organ involvement may result from a combination of paraprotein-dependent and -independent factors, and the therapeutic success requires the early recognition of all the pathogenetic factors involved. This case reminds that sometimes, to reach the right diagnosis, looking beyond the surface is mandatory. Moreover, in patients with not acute massive pulmonary embolism and intracardiac right masses, surgical pulmonary embolectomy should be promptly performed to preserve RV function and prevent pulmonary hypertension development. This case also demonstrated that both early diagnosis and prompt treatment with bortezomib and ASCT-based combinations can improve the prognosis of LCDD, even in patients with a severe disease at onset.

Abbreviations
MMI: Multiple myeloma; FLC: Free light chains; TTE: Transthoracic echocardiogram; RV: Right ventricle; LV: Left ventricle; CT: Computed tomography; IF: Immunofluorescence; LCDD: Light chain deposition disease.

Supplementary Information
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Additional file 1. Intracardiac thrombi. The video shows echocardiography performed before and after surgery.

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Authors’ contributions
The authors listed below have made substantial contributions to the intellectual content of the paper in the various sections described below. Conceptualization, M.A., S.I., B.B., F.P., F.C.; methodology, M.A., F.P., E.A., N.M., C.D.M., L.C., F.C., P.S.; writing—original draft preparation, M.A., S.I., B.B., F.C.; writing—review and editing, M.A., E.A., N.M., C.D.M., L.C., F.C., P.S.; supervision, M.A., F.P., C.D.M., P.S. All authors have read and agreed to the published version of the manuscript.

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