

Occurrence of Metachronous Multiple Myeloma in an Elderly Patient with Chronic Myeloid Leukemia in Treatment Free-Remission: A Case Report and Review of the Literature

<https://doi.org/10.62940/als.v13i3.4020>

Issue: Volume 13, Issue 3

Received: 13-10-2025

Revised: 22-08-2026

Accepted: 24-08-2026

Published online: 27-09-2026

Keywords: Immunoglobulin G, Multiple myeloma, Chronic myeloid leukemia, Bortezomib, Lenalidomide, Imatinib

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ABSTRACT

Background : Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of Philadelphia chromosome t(9;22) (q34;q11). Multiple myeloma (MM) is a clonal plasma cell proliferation. The co-existence of CML and MM is rarely reported in medical literature, and its pathogenesis remains poorly understood. We describe the unusual presentation of a CML patient who developed MM after approximately ~15 years of CML diagnosis, currently in treatment free remission.

Methods : We retrospectively reviewed the clinical data, imaging studies, laboratory investigations including serum protein electrophoresis, and routine molecular monitoring. A detailed literature review of reported CML and MM co-occurrences was also conducted. Informed patient consent was obtained.

Results: A 73-year-old male diagnosed with CML, currently in treatment-free remission (TFR) for the past 8 years, presented with new cardiac and spinal symptoms. A detailed diagnostic evaluation, including laboratory tests and imaging, revealed features of plasma cell dyscrasia, establishing a definitive diagnosis of metachronous MM. Bone marrow core biopsy, bone marrow aspirate revealed 35% to 40% plasma cells and 23% plasma cells, respectively. The immune-histochemistry was positive for CD38+, CD138+, CD56+, Beta-2 microglobulin (β_2 M) +, Kappa Light Chain.

Conclusion: In conclusion, this case elucidates the development of a second primary hematologic malignancy during extended CML treatment-free remission. It highlights the necessity of continuous comprehensive clinical investigation beyond routine BCR-ABL1 testing and suggests that monitoring serum protein electrophoresis may be clinically valuable in long-term TKI-treated patients.

INTRODUCTION

The Philadelphia (Ph) chromosome, caused by the t(9;22) (q34;q11) reciprocal translocation, produces the BCR-ABL1 hybrid fusion gene and causes chronic myelogenous leukemia (CML). Chronic myeloid leukemia (CML) affects 1–2/100,000 annually, with an average age of 65 at diagnosis [1]. Multiple myeloma (MM) affects lymphoid plasma cells. Multiple myeloma accounts for 1% of all cancers and approximately 10% of all hematologic malignancies [2, 3]. Each year, over 32,000 new cases are diagnosed in the United States, and almost 13,000 patients die of the disease [4]. The annual incidence rate is 5.6/100,000, and is frequently diagnosed at the age of 70 years [5]. The co-existence of MM and CML has been reported earlier and is an extremely rare event. A literature review shows that, since the early 1970s, there have been 30 such cases documented in the literature (

supplementary table 1

). The co-existence of such malignancies in such patients remains unanswered and further research insights are required for better understanding of its pathophysiology and outcomes. Here we describe the unusual case of an elderly male patient who was treated successfully for CML and developed MM after approximately 180 months (~15 years) post CML diagnosis.

METHODS

Case Report

Investigations

We describe the case of a 73-year-old man who had ischemic heart disease, diabetes mellitus, and hypertension in the past. Approximately 18 years ago (year 2006), he was diagnosed with CML. For almost 10 years, he received effective treatment with imatinib (year 2016). The CML treatment was discontinued eight years ago (year 2016), and patient was in complete remission (CR) till date. The patient had spinal degeneration changes and had cervical laminectomy two years ago. Patient residual myelopathy included limb stiffness, hand intrinsic muscle atrophy, and hyperreflexia. During current visit, patient complained of chest pain as well as upper and middle thoracic spinal pain on this particular occasion. The patient was admitted by the cardiology department. His cardiac enzymes and electrocardiogram (ECG) were within normal ranges. The ECG findings were suggestive of ventricular wall thickness which was indicative of infiltrative disease. Thoraco-abdominal aortic dissection was ruled out by a computed tomography (CT) chest angiography. However, it indicated a stable thoracic (T5) vertebral body compression fracture. Subsequent, magnetic resonance imaging (MRI) scans showed a compression fracture of the body of T5 with a posterior convex border and substantial marrow edema in the prevertebral soft tissue and dura. The T9 vertebrae also showed a heterogeneous marrow signal with focal enhancement. Heterogeneous marrow signals were also noted in the visualized portion of the sternum. The figure 1(a) for CT and (b) for MRI images depicting the T5 vertebral body fracture.

With no specific neurological impairments, he was fully conscious and oriented but had long-term cervical myelopathy. The neurosurgery team recommended applying thoracolumbar external brace and radiotherapy was recommended for his thoracic spinal lesions. He was further investigated by the hematology and oncology teams. The skeletal survey revealed multiple ill-defined lytic lesions involving the skull, spine, and the pelvic bones. The whole-body MRI demonstrated extensive bone marrow infiltration. Given the strong suspicion that the patient had MM, additional testing was sent to the laboratory for confirmation.

RESULTS

Diagnosis

A peripheral blood smear revealed no unusual findings, apart from a mildly toxic neutrophil granulation that suggested stress (see Fig 2: (a+b)). The bone marrow core biopsy revealed 35% to 40% plasma cells (see Fig 2: (c+d)), while the bone marrow aspirate differential cell count showed 23% of the plasma cells. The results showed multiple fractures and clinically evident, poorly defined lytic lesions, which were consistent with multiple myeloma (MM). The bone marrow aspirate immune-histochemistry results showed positive reaction for CD38+ and CD138+ (Fig. 3) and IgG kappa-restricted plasma cell dyscrasia. Serum levels of IgG, IgA, and IgM were 30.10 g/L (normal range: 6.103 to 16.16 g/L), 0.95 g/L (normal range: 0.8 to 3.0 g/L) and 0.40 g/L (normal range: 0.4 to 2.5 g/L), respectively. Subsequent analysis revealed a kappa

free light chain level of 27.70 mg/L (normal range: 3.3 to 19.4 mg/L), lambda free light chain level of 13.80 mg/L (normal range: 5.71 to 26.3) and ratio of serum kappa/lambda was 2.01 (normal range: 0.26 to 1.65).

There was no Bence Jones protein present. Investigations like serum creatinine, hemoglobin level, and serum calcium, serum albumin all stayed within the normal range (*Supplementary table 2*).

The diagnosis of multiple myeloma was based on the presence multiple bone fractures, 35% to 40% plasma cells in the bone marrow core biopsy, 23% plasma cells in bone marrow aspirate, positive immune-histochemistry (CD38+, CD138+, CD56+, Beta-2 microglobulin (β_2M) +, Kappa Light Chain) (Fig. 4).

There was no evidence of a numerical abnormality involving chromosomes 3, 5, or 11. There was no evidence of an IGH/ CCND1 rearrangement associated with the chromosomal abnormality t(11;14)(q13;q32). There was no indication that the IGH gene had been rearranged along chromosome 14's long arm. The 17p deletion chromosomal abnormality was not linked to any evidence of a *TP53* gene deletion. The final diagnosis for the patient was IgG kappa-restricted MM.

Treatment

The patient was ultimately diagnosed with IgG-k restricted MM (December-2021), revised International Staging System [6] (R-ISS) stage III (suggestive of 29-months progression free survival), and treatment for newly diagnosed MM lesions, which does not qualify for a transplant, began with DRd protocol [Cycle 1 and 2: (i) Daratumumab, 16 mg/kg (IV), day 1, 8, 15, 22; (ii) Lenalidomide, 25 mg ONCE a day (PO), days 1 to 21; (iii) Dexamethasone, 20 mg ONCE a day, day 1 and 2, 8, 9, 15, 16, 22 and 23; Cycles 3 to 6: (i) Daratumumab, 16 mg/kg (IV), day 1 and 15; (ii) Lenalidomide, 25 mg ONCE a day (PO), day 1 to 21; (iii) Dexamethasone, 20 mg ONCE a day, day 1 and 2, 15, 16; Cycle 7 and further cycles: (i) Daratumumab, 16 mg/kg (IV), day 1; (ii) Lenalidomide, 25 mg ONCE a day (PO), day 1 to 21; (iii) Dexamethasone, 20 mg ONCE a day, day 1 and 2].

Follow-up and outcome

As of the last follow-up (June-2024), the patient tolerated the treatment regimen, DRd, with no adverse effects. The latest serum kappa/lambda ratio tested as of November-2024 was 2.23 (reference ratio range: 0.26 ~ 1.65). The serum kappa lambda ratio trend since the diagnosis of MM (December-2021) is highlighted in *supplementary table 2*.

The patient remained off CML treatment, on remission till date. Initial BCR/ABL quantification was performed at the time of current admission (December-2021), and its level was 0.015% (IS-NCN), which was suggestive of major molecular response (MMR), defined as value of IS-NCN: <0.05. Consequently, the BCR/ABL values tested, in a most recent to oldest order were as following: June-2024: BCR/ABL- 0.0093% (IS) & MR: 4.03; August-2023: BCR/ABL- 0.035% (IS) & MR: 3.46; May-2023: BCR/ABL- 0.050% (IS) & MR: 3.30; August-2022: BCR/ABL- 0.026% (IS) & MR: 3.59.

Figures

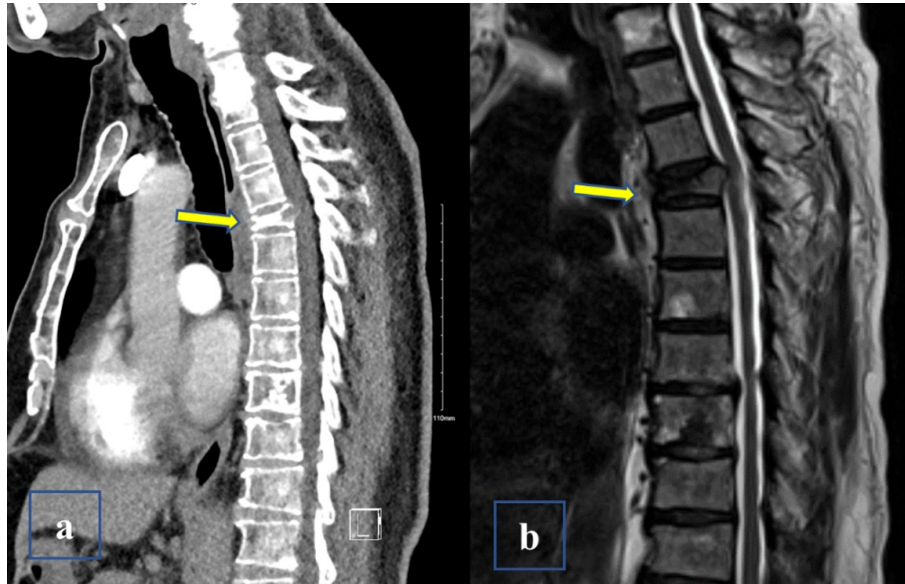


Figure 1: (a) A CT image showing thoracic (T5) stable vertebral body compression fracture, yellow arrow (b): An MRI image of the thoracic spine showing compression fracture of the body of T5 with a posterior convex border and substantial marrow edema in the prevertebral soft tissue and dura, yellow arrow.

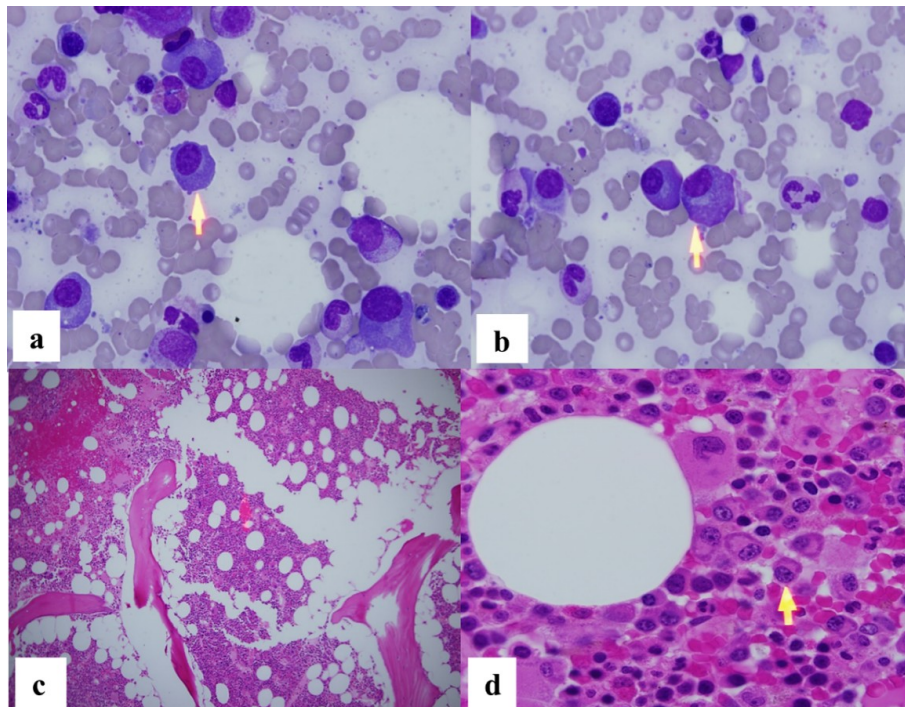


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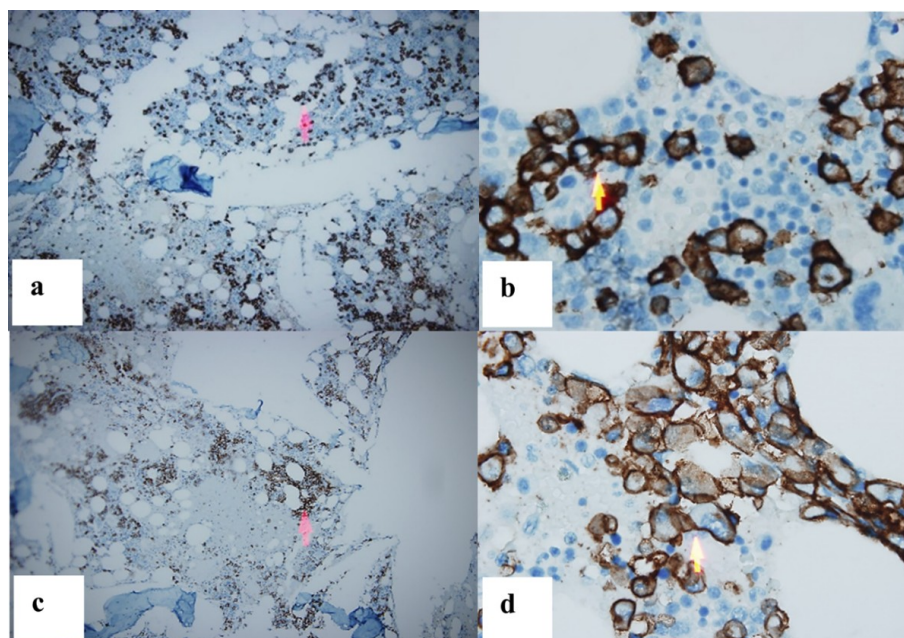


Figure 3: Bone marrow aspirate immunohistochemistry staining results showing positive reaction for CD-38+ (a+b) and CD-138+ (c+d).

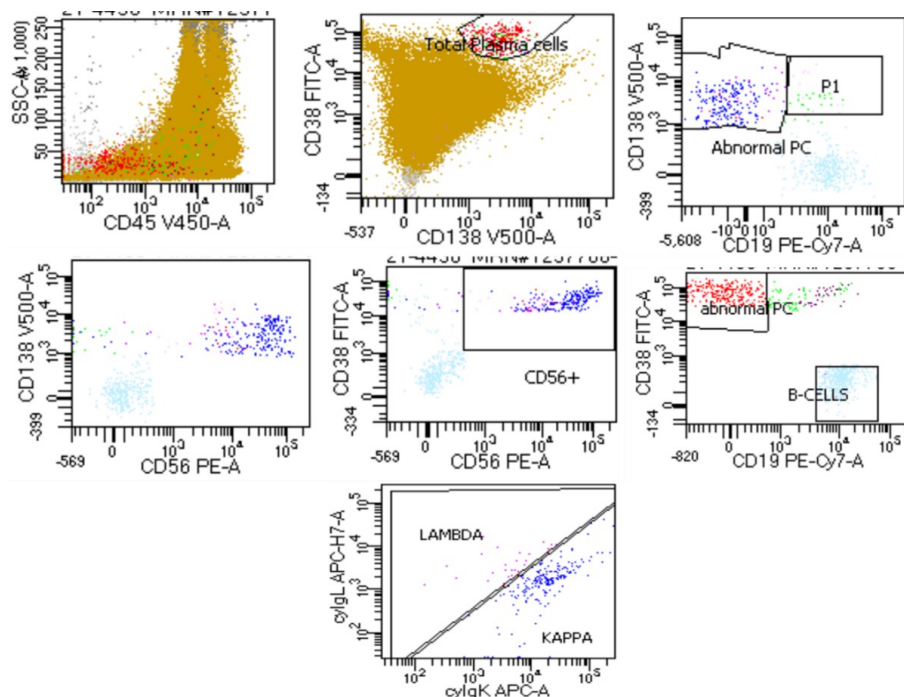


Figure 4: Flow Cytometry findings revealed CD45-negative, CD38+, CD138+, CD56+, B-2 Microglobulin+, Kappa Light Chain Restricted. Consistent with relapse Multiple Myeloma.

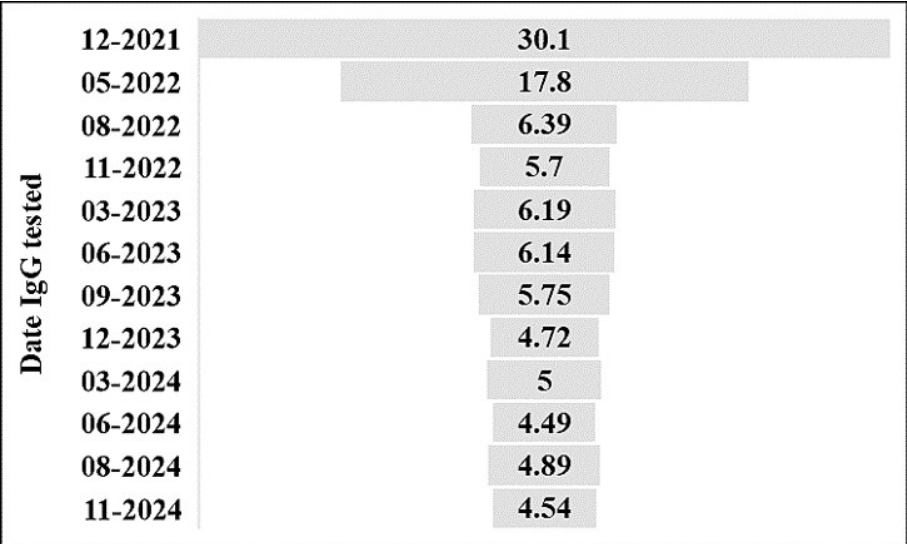


Figure 5: Quantification of IgG in g/L (normal range: 6.103 to 16.16g/L) in the course of treatment (daratumumab, lenalidomide, dexamethasone (DRd).

DISCUSSION

The coexistence of MM and CML in the same patient is an extremely rare event. In the literature, the incidence of synchronous or metachronous cancers has been reported to range from 0.73-11.7% [7]. Only a few studies have examined the incidence of MM and CML in the same patient, either concurrently or sequentially [8]. Since 1970, thirty cases have been documented in scientific literature as tabulated in the *supplementary table 1* [9]. Thus, it is worthwhile to investigate the etiology and clinical features of these patients in more detail. The precise etiology of the two concomitant malignancies is not fully understood. There are several hypotheses like host-specific characteristics, treatment of pre-existing malignancy, exposure to radiations and environmental carcinogens; furthermore the role of epigenetics may also an important role. Although there is no clear explanation or biological link for the coexistence of these two distinct hematological malignancies, a neoplastic transformation of pluripotent stem cells has been proposed as one possible cause [10]. At the time of diagnosis of CML, the patient age was 55 years. At the age of 70 years, patient was diagnosed with a new primary cancer, MM, almost 15 years after CML diagnosis. The patient history included a standard dosage regimen for CML treatment i.e., Imatinib and was on treatment free remission for the last 60 months prior to MM diagnosis.

The patient was started on DRd combination treatment regimen for MM as he was not eligible to receive bortezomib due to pre-existing neuropathy. In an open-label phase 3 trial (MAIA), the researchers studied the effect Daratumumab with lenalidomide plus dexamethasone (DRd) vs. lenalidomide plus dexamethasone (Rd) alone [11], and after a median follow-up of 56 months found that the addition of daratumumab resulted in a CR or better response (51 vs. 30%, improved 5 years PFS (53 vs. 29%; HR 0.53, 95% CI 0.43-0.66) and an Improved OS (66 vs. 53%, HR 0.68, 95% CI 0.53-0.86), respectively [12].

The monoclonal IgG value at the time of diagnosis was 30.1 g/ L and was still not within reference range as of May-2022 (after 5.5 cycles of DRd). The monoclonal IgG level returned back to normal after 8.2 cycles of DRd (August-2022) and all values tested afterwards were in approximately normal range (Fig. 5). The serum kappa-lambda ratio, which was trending within normal limits, was tested high as per last testing (November-2024), which might reflect the beginning of disease progression (refer to *supplementary table 2* for detailed periodic testing).

Upon reviewing the current literature, some interesting patterns (n=30) of occurrence of two types of cancer, CML and MM, have been reported as summarized in *supplementary table 1*. The diagnosis of CML preceded that of MM in 10 out of 30 cases, 33.3% (patients 1-10; *supplementary table 1*); the following 10 patients, 33.3%, (11-20; *supplementary table 1*) presented with a synchronous pattern i.e., simultaneous detection of CML+MM; the diagnosis of MM preceded that of CML in ten cases, 33.3% (patients 21-30; *supplementary table 1*).

In the pattern CML→MM (patients 1-10; *supplementary table 1*), the interval between the diagnosis of each disease ranged from 3 to 137 months. Our case is notable as this interval was 180 months. Among previously reported cases, n=18/30, 60% patients had immunoglobulin G myeloma, 8 (26.7%) patients had immunoglobulin A myeloma, 3 (10%) patients had light chain disease (Bence Jones protein) and one patient (3.3%) demonstrated immunoglobulin D myeloma. Nine of the ten patients (90%) who were first diagnosed with CML had been treated with TKIs, imatinib mesylate, for CML before MM developed. Seventy percent (70%) of the patients who first developed MM received chemo- radiotherapy for MM (n=7/10). The occurrence of CML and MM in the same patient is unusual; it may suggest a correlation between the two separate hematological malignancies rather than an incidental occurrence.

Several different pathophysiologies theories exist describing the occurrences of synchronous or metachronous of these two types of cancers (CML and MM). Firstly, in advanced stages of CML disease, blast crisis, a third of cases have lymphoid transformation, which favors the existence of a single stem cell that can differentiate into both myeloid and lymphoid cell lineages, with a possibility to transform along the lympho-plasmacytic and myeloid lineages, resulting in CML and MM [13, 14]. While emerging evidence suggests a potential genetic link between Chronic Myeloid Leukemia (CML) and Multiple Myeloma (MM) – specifically regarding the PSORS1C1-rs2285803 locus – the overlap remains poorly understood [15]. Recent research suggests a possible shared genetic background between myeloproliferative neoplasms (MPNs) and multiple myeloma (MM) [15], according to an exploratory study carried out by a European multicenter. There is mixed data regarding imatinib impact on myeloma cells. Two studies have shown that imatinib inhibits myeloma cell proliferation in vitro by stopping the cell cycle progression. One study found that imatinib slightly stimulated MM cell proliferation through activating the Erk1 and Erk2 mitogen- activated protein kinases (MAPKs) route [16, 17]. To establish a biological connection between CML and MM and to precisely identify the function of imatinib in the development of MM, more investigation is needed.

In conclusion, this case demonstrated that the two hematological malignancies (MM and CML) could coexist in the same patient. This is an extremely rare event, and the exact cause is undetermined and could be multifactorial, with only a few cases reported in the literature thus far. Moreover, further research is needed to explore the exact cause of the occurrence of such malignancies.

FUNDING STATEMENT

This work has not received any form of financial support or funding.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

Additional files

Supplementary table 1: A summary of chronic myeloid leukemia and multiple myeloma cases reported in the literature

Supplementary table 2: Summary of trending of different laboratory examinations overtime, including: β -2- Microglobulin, Serum Immunoglobulin G, Serum Immunoglobulin A, Serum Immunoglobulin M, Serum Free Kappa, Serum Free Lambda, Serum Free Kappa / Free Lambda Ratio, Serum Calcium, Blood Hemoglobin, Serum Creatinine, Serum Albumin, Blood WBC count and LDH. kappa/lambda ratio trend analysis is also summarized.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Abdulkareem AlGarni, Hammad Ul Haq Qureshi, Munirah Alabdulqader, Yahya Alzahrani and Muhammad Absar did the literature review and drafted the manuscript.

Munirah Alabdulqader, Abdulmalik Alabdulqader, Muhammad Absar, Musa Mbahi and Yahya

Alzahrani prepared the figures and figure legends.

Abdulkareem AlGarni discussed with the patient about the publication and obtained the written consent.

Abdulkareem AlGarni Hammad Ul Haq Qureshi, Abdulmalik Alabdulqader, Musa Mbahi, Muhammad Absar, and Abdullah Alruwaili edited the manuscript.

Abdulkareem AlGarni and Hammad Ul Haq Qureshi supervised this work.

All authors have read and approved the final manuscript.

ACKNOWLEDGMENT

We extend our special thanks to all healthcare workers involved in the care of this patient.

ETHICS STATEMENT

Informed consent

Written informed consent was obtained from the patient for the publication of the present case report and any accompanying images.

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