


# Double trouble: A case of synchronous presentation of acute myeloid leukaemia and multiple myeloma

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Malignancies following successful chemotherapy for various malignant diseases, including multiple myeloma (MM), are well known and documented. The occurrence of acute myeloid leukaemia (AML) after chemotherapy for MM with alkylating agents is well described; however, simultaneous occurrence of the two entities with no prior therapy is extremely rare. We describe a case of an elderly patient with no previous exposure to chemotherapy, who was diagnosed with both MM and AML concurrently. Very few similar cases have been described in the literature.

**Keywords:** multiple myeloma; acute myeloid leukaemia; flame cells; synchronous; chemotherapy.

## Case report

An 80-year-old patient was referred to our division for a bone marrow examination with a clinical history of pancytopenia. He had multiple co-morbidities (hypertension, benign prostatic hyperplasia, previous myocardial infarction and gastro-esophageal reflux disease) and was HIV negative. Of significance was the history of a monoclonal gammopathy of undetermined significance (MGUS), which was diagnosed 8 years prior and confirmed as still an MGUS 4 years later.

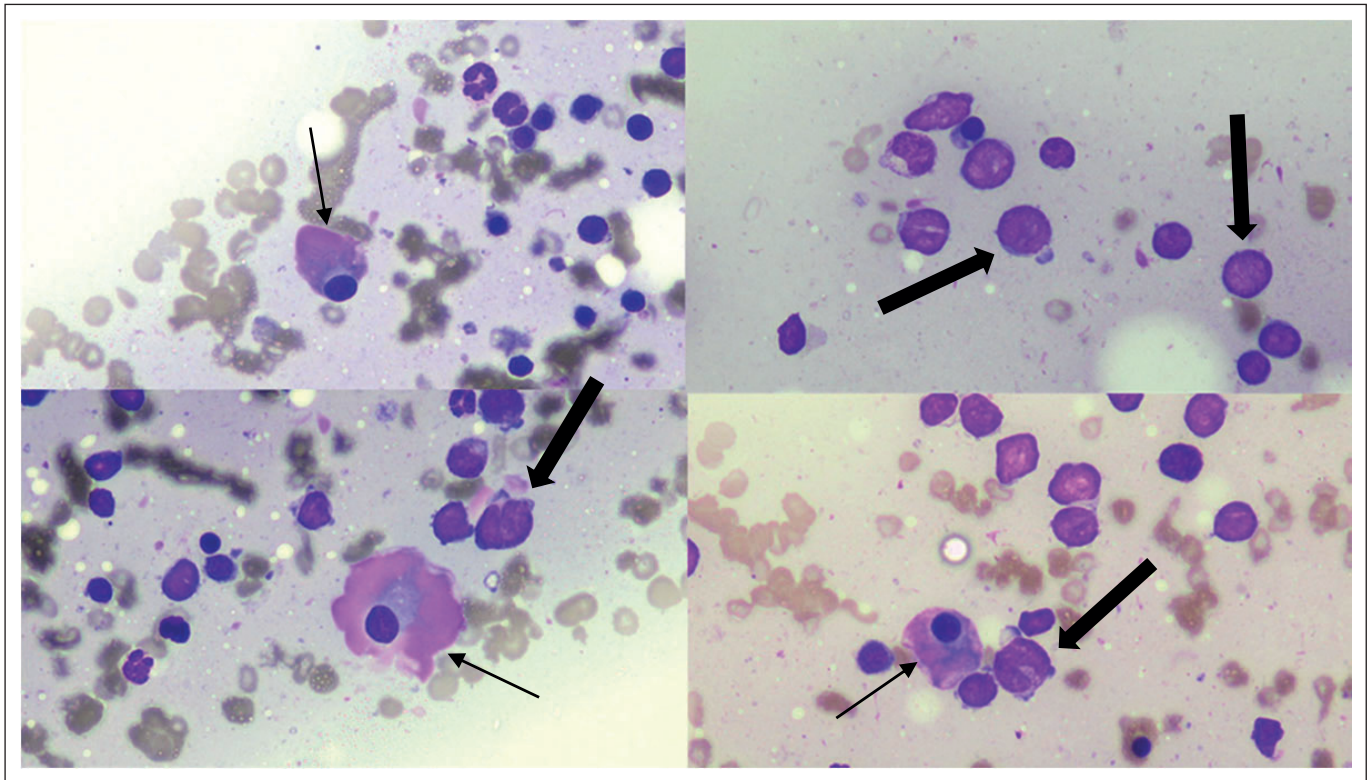
Laboratory tests revealed normal renal function, normal calcium levels and no nutritional deficiencies with normal vitamin B12 and folate levels. A full blood count demonstrated normocytic anaemia with a haemoglobin of 7.8 g/dL and thrombocytopenia with a platelet count of  $49 \times 10^9/L$ . The white cell count was  $2.01 \times 10^9/L$  with circulating blasts reported.

The bone marrow aspirate showed 27% blasts (Figure 1) with some granulocytic maturation demonstrated by 13% segmented neutrophils; 8% plasma cells were counted on average, the majority of which were flame cells (Figure 1). The good-quality trephine biopsy revealed a hypercellular bone marrow for age, with appreciable foci of blasts in areas and an interstitial increase in plasma cells. CD34 and CD138 immunohistochemistry demonstrated two abnormal populations, 40% myeloblasts and 30% plasma cells, respectively.

Flow cytometry was performed on the bone marrow aspirate and  $\pm 20\%$  blasts were evident, expressing the following immunophenotype: CD45, CD34, CD117, HLA-DR, CD38, CD13 and cMPO with aberrant TdT, which was in keeping with acute myeloid leukaemia (AML). B-cell, T-cell and monocytic markers were not expressed. Karyotyping revealed numeric as well as structural abnormalities, namely, a trisomy 8 and a deletion on chromosome 20 (47, XY, +8, del(20)(q11.20)). Fluorescent *in situ* hybridisation (FISH) studies similarly revealed trisomy 8 (60.5%) and deletion 20q12 (95%).

IgA lambda clonality was demonstrated on serum immunofixation and urine protein electrophoresis. No lytic lesions were reported on radiological examination; however, the more sensitive magnetic resonance imaging was not carried out. The presence of 30% clonal bone marrow plasma cells and a myeloma defining event met the International Myeloma Working Group diagnostic criteria for multiple myeloma (MM) (Box 1).<sup>1</sup> Because of the concomitant AML, the anaemia cannot be definitively attributable to the proliferative clonal plasma cells, in which case smouldering MM would be more accurate. However, there is no accurate way to discount that the anaemia may be due to the clonal plasmacytosis and is likely attributed to both conditions.

A diagnosis of AML with concurrent MM that had progressed from MGUS was established based on the above findings and detailed history of documented MGUS. Unfortunately, the patient demised soon after the diagnosis was made.



**FIGURE 1:** Bone marrow aspirate showing blasts (thick arrows) and flame cells (thin arrows).

**BOX 1:** International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma.

**Multiple Myeloma**

Clonal bone marrow plasma cells > 10% or plasmacytoma

PLUS 1 or more of the following myeloma defining events:

- $\geq 1$  CRAB<sup>†</sup> feature
- $\geq 60\%$  clonal bone marrow plasma cells
- $\geq 100$  involved: uninvolved serum free light chain ratio
- > 1 focal magnetic resonance imaging lesion

**Smouldering Multiple Myeloma**

M protein > 30 g/L (serum) OR > 500 mg/24 hour (urine) AND/OR 10% – 60% clonal bone marrow plasma cells

PLUS

Absence of myeloma defining events

Source: Modified from Rajkumar et al.<sup>1</sup>

<sup>†</sup>, CRAB = C, hypercalcaemia; R, renal insufficiency; A, anaemia; B, bone lesions.

## Discussion

Reactive plasmacytosis may occur as a paraneoplastic syndrome in certain malignancies, including Hodgkin and non-Hodgkin lymphomas, some carcinomas and AML after chemotherapy. It is a rare finding in cases of AML at diagnosis but has been documented,<sup>2,3,4</sup> and these cases usually have less than 10% plasma cells; however, rare cases with > 20% reactive plasma cells have been reported.<sup>2</sup> As such, a finding of bone marrow plasmacytosis in a newly diagnosed AML presents a diagnostic challenge and warrants further investigations to exclude a concomitant clonal proliferation.

A few cases of dual presentation of MM and AML have been reported in the literature. Acute myeloid leukaemia occurring after MM treatment with chemotherapy containing alkylating

agents is more well described, with melphalan use considered to be the main cause of the secondary malignancy<sup>5</sup> and lenalidomide also implicated to be causative.<sup>6,7</sup> Acute myeloid leukaemia diagnosed simultaneously with MM is much rarer, with a few cases of AML occurring in chemotherapy-naive MM reported in literature.

No clear mechanism underlying the development of AML and MM without prior exposure to chemotherapy has been elucidated; however, a few have been suggested as possibilities. Patient and disease-related factors have to be considered to play a significant role in the development of the dual haematological malignancies. Postulated mechanisms include a disorder of multipotent stem cells, exposure to common environmental or radiation risk factors and repeated infections, particularly in patients with myeloma, with eventual development of a leukaemic clone.<sup>8,9,10</sup>

In addition, MM is a slowly progressive disorder, and disease evolution from MGUS to MM is associated with an immunosuppressive milieu characterised by dysfunction of immune effector cells, loss of effective antigen expression and an increase in immunosuppressive cell types.<sup>11</sup> This decreased immune surveillance fosters immune escape of neoplastic cells and tumour growth, and it may result in failure to eliminate incipient leukaemic clones.<sup>9,10,11</sup> Our patient had been diagnosed with MGUS 8 years prior to presenting with both MM and AML. This is in keeping with the findings by Mailankody et al. that patients with MGUS, particularly IgA/IgG, have an increased risk of developing AML/myelodysplastic syndrome (MDS).<sup>5</sup>

Lu-Qun et al. have speculated that multiple gene mutations may be involved in the occurrence of the two malignancies simultaneously, particularly deletions of RB-1, TP53 and 1p32, which were demonstrated in the plasma cell population of their patient.<sup>12</sup> The trisomy 8 and deletion 20q demonstrated by both FISH and cytogenetics in our patient likely represent the leukaemic clone as the aspirate had fewer plasma cells than the trephine, and the abnormalities are associated with myeloid malignancies rather than a plasma cell neoplasm.<sup>13</sup>

Due to the rarity of the concurrent presentation of AML and MM, there is no established treatment modality. Because AML is the more aggressive of the two malignancies, patients are often treated with AML regimens. These typically include anthracyclines, which have some efficacy against myeloma cells in addition to their anti-leukaemic effects. Despite the treatment with these regimens, these patients have a poor outcome, with a reported median survival of < 5 months.<sup>14</sup> A single patient has been reported to survive after successfully undergoing an allogeneic stem cell transplant.<sup>15</sup>

## Conclusion

Multiple myeloma is a disease of the elderly with a median age at diagnosis of ~70 years, whilst the incidence of MGUS also increases with age.<sup>13</sup> The risk of progression to MM is 1% per year, with IgAMGUS having a slightly higher progression risk. Given the patient's history of MGUS, it is possible that the AML might have developed coincidentally in the background of the MGUS, progressing to MM. Similar reported cases, however, highlight the possibility of yet-to-be-defined mechanisms at play, with host factors probably playing a key role.

The altered bone marrow microenvironment that results in providing a supportive niche for emerging neoplastic clones and suppression of the host immune system resulting in the escape and progression of incipient clones begin to emerge as possible mechanisms for consideration in the development of dual malignant neoplasms.

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## Competing interests

The author has declared that no competing interest exists.

## Authors' contribution

The author declares that she is the sole author for this article.

## Ethical consideration

Ethical clearance for the study was obtained from the Health Research Ethics Committee of Stellenbosch University on 27/07/2020. Ethical Clearance number: C20/07/022.

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## Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

## Disclaimer

The views and opinions expressed in this article are those of the author and do not necessarily reflect the official policy or position of any affiliated agency of the author.

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