CASE REPORT

Synchronous Plasma Cell Myeloma and Acute Myeloid Leukemia in a Therapy-Naïve Patient: A Rare Occurrence

Rajesh Kumar¹ · Vishrut K. Srinivasan¹ · Prashant Sharma² · Ritu Aggarwal³ ·
Gaurav Prakash⁴ · Pankaj Malhotra⁴ · Neelam Varma²

Received: 27 October 2015 / Accepted: 7 December 2015 / Published online: 17 December 2015
© Indian Society of Haematology & Transfusion Medicine 2015

Abstract Plasma cell proliferations in patients with acute myeloid leukemia (AML) are rare, whether at presentation or during or after therapy. Interpretation requires correlation with the clinical background, drug history as well as inputs from tests for monoclonal gammopathy and end-organ damage. The major diagnostic issues stem from excluding myeloma alone with a plasmablastic morphology that mimics AML as well as reactive or polyclonal plasmacytosis occurring in a bonafide case of AML alone before rendering a rare diagnosis of true dual pathologies. We report a rare case of concurrent AML and plasma cell myeloma in a 55-year-old lady that posed a significant diagnostic challenge. The patient had significant co-morbidities complicating the clinical picture and was treatment-naïve at the time of diagnosis. Our approach to confirming the diagnosis, as well the challenges faced in

flow cytometric analyses are highlighted. The pathogenesis of such dual pathologies remains unresolved, although various conjectures and theories have been propounded in literature.

Keywords Acute myeloid leukemia · Plasmacytosis · Multiple myeloma · Plasma cell myeloma

Introduction

Plasmacytosis is known to occur in AML, especially after the initiation of therapy. Plasma cell numbers can be increased significantly, in certain cases, to levels that simulate plasma cell myeloma/multiple myeloma [1]. Hence, it is imperative to establish a definitive diagnosis of a dual pathology for a better guidance of further management and prognostication of such patients.

The case was presented as a poster at the 19th AIPNA-ICP International CME held at PGIMER, Chandigarh from 6 to 8 February, 2014.

✉ Prashant Sharma
prashant.sh@gmail.com; sharma.prashant@pgimer.edu.in

Rajesh Kumar
dr_rajesh996@yahoo.co.in

Vishrut K. Srinivasan
vishrut.ks@gmail.com

Ritu Aggarwal
ritu_immunopath@yahoo.co.in

Gaurav Prakash
drgp04@gmail.com

Pankaj Malhotra
malhotrapankaj@hotmail.com

Neelam Varma
varmaneelam@yahoo.com

¹ Pathology Group Departments, Postgraduate Institute of Medical Education and Research (PGIMER), Research Block A, Chandigarh 160012, India

² Department of Hematology, Research Block-A, Postgraduate Institute of Medical Education and Research (PGIMER), Sector-12, Chandigarh 160012, India

³ Department of Immunopathology, Postgraduate Institute of Medical Education and Research (PGIMER), Research Block A, Sector 12, Chandigarh 160012, India

⁴ Department of Internal Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Nehru Hospital, Chandigarh 160012, India

Case Report

A 55-year-old lady presented with a 2-month history of fever, fatigue and weakness. Over the last 1 week, she had developed high-grade fever, prostration, dysphagia and difficulty in opening mouth. On general examination, the toxic-looking patient had pallor and poor oral hygiene. A large ulcer with whitish margins was identified extending medially from the right side of hard palate, and destroying hard palate. No organomegaly or lymphadenopathy were identified.

Her initial hemogram showed pancytopenia with hemoglobin 73 g/L, total leukocyte count $3.0 \times 10^9/\text{L}$ and platelet count $34 \times 10^9/\text{L}$. Peripheral blood film showed rouleaux formation with normocytic normochromic red cells. The differential count was 4 % blasts, 2 % neutrophils, 04 % monocytes and 90 % lymphocytes. Bone marrow aspirate smears were hypercellular and showed 60 % myeloid blasts, 37 % plasma cells and 3 % erythroid cells (Fig. 1a). The blasts were 2–4 times the size of mature lymphocytes showing irregular to indented nuclei with 1–3 prominent nucleoli, opened-up chromatin and scanty to moderate amount of basophilic, scantily granular cytoplasm. Occasional Auer rods were seen that were strikingly positive on cytochemical staining for myeloperoxidase (Fig. 1b). The 37 % plasma cells ranged from normal to large in size. A few showed nuclear enlargement, multinucleation and prominent nucleoli (Fig. 1c). Erythroblasts showed significant dyserythropoiesis (30 %) in the form of nuclear budding and bi-nucleation (Fig. 1c). Only an occasional megakaryocyte with normal morphology was noted.

Flow cytometric immunophenotyping was performed on the bone marrow and the blast population within the dim-CD45/low side scatter region was gated. These cells were positive for CD34, MPO, CD13 and CD117. Plasma cells expressing bright CD38 and low side scatter were gated separately, and a gating strategy based on CD45/forward scatter plot was adopted to ensure that there was no cross contamination across the two abnormal cell populations. The plasma cells were positive for CD45 and negative for CD19 (Fig. 2a–h illustrate the analysis strategy applied). Reverse transcriptase polymerase chain reactions (RT-PCR) were negative for inv(16), t(8;21) and t(15;17).

Serum protein electrophoresis revealed a prominent monoclonal band (M-band; 6.08 g/dL) in the gamma region in the background of hypogamaglobulinemia (Fig. 1d, lane 1 on the left). Immunofixation confirmed monoclonality for IgG with kappa restriction (Fig. 1d). Renal function tests were normal. The total serum protein was 8.69 g/dL with albumin 2.32 g/dL. Serum calcium level was 8.28 mg/dL after correction for

hypoalbuminemia. Serum creatinine (0.69 mg/dL), urea (34.21 mg/dL), sodium (144.70 mEq/L) were within respective normal ranges.

Histopathology of the palatal lesion showed severe neutrophilic and plasmacytic infiltrates suggesting vasculitis. Although an initial possibility of Wegener granulomatosis was suggested, this was revised on consideration of the entire clinical background to possibly represent a fulminant necrotizing infectious process. The final diagnosis therefore was AML without maturation (FAB—AML M1, WHO—not otherwise specified) with co-existing plasma cell myeloma.

The patient and her family were counselled regarding treatment options, costs and possible prognosis. They elected to undergo palliative care closer to her home and she was discharged in a poor but stable general condition. No follow-up is available.

Discussion

Bone marrow plasmacytosis is a well-described pathological process known to occur in a variety of conditions such as infections, autoimmune diseases, cirrhosis of liver, as a paraneoplastic syndrome in various neoplasms such as Hodgkin and non-Hodgkin lymphomas and rarely, in acute leukemias [2–4].

Plasmacytosis in acute leukemias, even if present, is most often mild and does not exceed 10 %. It may occur post-therapy, especially as a relative increase in a hypocellular marrow. A few previous cases of more pronounced plasmacytosis at the time of diagnosis of AML have been described in literature. Some of these were reactive proliferations [4, 5]. In the 149 cases of AML studied by Rosenthal et al. [6], only 2 showed plasmacytosis in excess of 20 %. Reactive plasmacytosis is suggested by the presence of polyclonality, a normal kappa/lambda chain ratio and less reliably, by morphological features of plasma cells which are exclusively mature forms and show mainly perivascular distribution [5].

When observed in acute leukemias, it is imperative to differentiate reactive plasma cell proliferations from the monoclonal gammopathies in order to guide the optimal management of the patient with rare dual haematological malignancies. This differentiation poses a diagnostic challenge and should be confirmed by further ancillary techniques rather than relying only on morphology in attempts to cut costs.

Concomitant occurrence of dual hematological neoplasms in the same patient is an exceptional event. Simultaneous occurrence of plasma cell myeloma and acute myeloid leukemia is rarely described previously. The

Fig. 1 **a** Bone marrow showing 60 % blasts and 37 % plasma cells (MGG, $\times 1000$). **b** The blasts were positive for cytochemical myeloperoxidase (MPO) including distinctive positivity in the Auer rods (DAB chromogen with hematoxylin counterstain, $\times 1000$). **c** Plasma cells were large and had prominent nucleoli.

Dyserythropoiesis was present in 30 % erythroblasts (black arrows) (MGG, $\times 1000$). **d** Serum protein immunofixation electrophoresis showed that the prominent M-band with background hypogammaglobulinemia (lane T on the left) corresponded to IgG and kappa light chains

majority of patients had history of treatment for myeloma and the leukemia occurred secondary to therapy. Only a few reports of concomitant myeloma with acute monocytic/monoblastic [7, 8] and myelomonocytic leukemia, [9–14] AML M2 (FAB) [15] acute promyelocytic leukemia [16] and AML-NOS [17, 18] have been described.

In the index case, the clinical, radiological and biochemical parameters were not suggestive of myeloma and hence the same was not suspected clinically. Plasma cells could have been explained away due to the clinically obvious underlying acute-on-chronic infection. However, monoclonality displayed by these plasma cells on serum protein electrophoresis ('M'-band/spike), immunofixation (kappa-light chain restriction) and immunophenotyping clinched the diagnosis of myeloma.

Reactive marrow plasmacytosis is a physiological response to antigenic stimulation [2, 3]. The exact

mechanism of this bone marrow plasmacytosis has not yet been addressed, although role of a paracrine growth factor has been proposed. A study by Wulf et al. [5], suggests that production of interleukin 6 by the myeloblasts may drive the plasma cell proliferation.

A shared pathogenesis, if any, of concurrent multiple myeloma and acute myeloid leukemia is not known. A few hypotheses describe these as disorders of multipotent stem cells [7, 9] that occur due to continuous exposure to some environmental risk factors and infection or other antigenic stimuli [7, 19]. Another explanation relies on the fact that multiple myeloma is a slowly evolving disease with a resultant decrease in immune surveillance. Incipient leukemic clones might escape immune elimination and the resulting AML may bring the pre-existing myeloma to clinical attention [19]. The prognosis of such patients previously described remains uniformly poor. No definite

Fig. 2 The gating strategy was adapted to capture both the neoplastic cell types. **a, b.** First, the blasts (*red*) were gated on FSC-SSC as large cells with low side scatter. **c** Then the FSC-CD45 plot was used to discriminate the plasma cells (*yellow*) from lymphocytes (*pink*).

d Plasma cells were CD38 bright and CD19 neg. **e** Blasts were CD34 positive. **f** Plasma cells were aberrantly positive for CD117. **g** Blasts expressed CD13 and CD33 and were negative for CD11c and CD64 (**h**) (color figure online)

drug therapy has been described. There are case reports of successful allogeneic stem cell transplantation [20] although that potentially curative treatment option may be unfeasible in these often critically ill patients.

Conclusion

A combined mechanism for the pathogenesis of AML and myeloma remains speculative, since the postulated cells of origin are different. The index case represents an exceptionally rare chance occurrence. However, it does illustrate the challenges faced by diagnostic hematopathologists in work-up of patients with haematological malignancies, and highlight the need for a high index of suspicion and the importance of inter-disciplinary working while chasing morphological clues.

Compliance with Ethical Standards

Conflict of interest All contributing authors declare no conflicts of interest.

Ethical Standard All procedures performed in this report of a single case involving a human participant were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was not obtained from the individual patient described in the case report since she could not subsequently be contacted in spite of our best efforts. We submit that

this requirement be waived as no information that can reveal the patient's identity is included in this manuscript so as to protect her privacy.

References

1. Al-Shughair N, Al-Dawsari G, Gyger M et al (2007) Clinical significance of plasmacytosis in the day +14 bone marrow of patients with acute myeloid leukaemia undergoing induction chemotherapy. *J Clin Pathol* 60:520–523
2. Hyun BH, Kwa D, Gabaldon H et al (1976) Reactive plasmacytic lesions of the bone marrow. *Am J Clin Pathol* 65:921–928
3. Liu CT, Dahlke MB (1967) Bone marrow findings of reactive plasmacytosis. *Am J Clin Pathol* 48:546–551
4. Gavarotti P, Boccadoro M, Redoglia V et al (1985) Reactive plasmacytosis. Case report and review of the literature. *Acta Haematol* 73:108–110
5. Wulf GG, Jahns-Streubel G, Hemmerlein B et al (1998) Plasmacytosis in acute myeloid leukemia: two cases of plasmacytosis and increased IL-6 production in the AML blast cells. *Ann Hematol* 76:273–277
6. Rosenthal NS, Farhi DC (1994) Reactive plasmacytosis and lymphocytosis in acute myeloid leukemia. *Hematol Pathol* 8:43–51
7. Luca DC, Almanaseer IY (2003) Simultaneous presentation of multiple myeloma and acute monocytic leukemia. *Arch Pathol Lab Med* 127:1506–1508
8. Murukutla S, Arora S, Bhatt VR et al (2014) Concurrent acute monoblastic leukemia and multiple myeloma in a 66-year-old chemotherapy-naïve woman. *World J Oncol* 5:68–71
9. Cleary B, Binder RA, Kales AN et al (1978) Simultaneous presentation of acute myelomonocytic leukemia and multiple myeloma. *Cancer* 41:1381–1386
10. Pasqualetti P, Colantonio D, Casale R et al (1990) Simultaneous presentation of multiple myeloma and acute myelomonocytic

- leukemia in the absence of previous chemotherapy. Description of a case and review of the literature. *Minerva Med* 81:487–493
11. Raz I, Polliack A (1984) Coexistence of myelomonocytic leukemia and monoclonal gammopathy or myeloma. Simultaneous presentation in three patients. *Cancer* 53:83–85
 12. Annino L, Martino P, Barsotti P et al (1980) Multiple myeloma and acute myelomonocytic leukemia: simultaneous occurrence without previous chemotherapy. *Acta Haematol* 64:195–200
 13. Tursz T, Flandrin G, Brouet J-C et al (1974) Simultaneous occurrence of acute myeloblastic leukaemia and multiple myeloma without previous chemotherapy. *Br Med J* 2:642–643
 14. Parapia L, Abbott CR, Masters G et al (1982) Simultaneous presentation of acute myelomonocytic leukaemia and multiple myeloma. *Acta Haematol* 68:153–156
 15. Shukla J, Patne SC, Singh NK et al (2008) Simultaneous appearance of dual malignancies of hematopoietic system-multiple myeloma and acute myeloid leukemia. *Indian J Pathol Microbiol* 51:118–120
 16. Lim J, Kwon GC, Koo SH et al (2014) A case of acute promyelocytic leukemia concomitant with plasma cell myeloma. *Ann Lab Med* 34:152–154
 17. Attili S, Lakshmaiah KC, Madhumati M et al (2006) Simultaneous occurrence of multiple myeloma and acute myeloid leukemia. *Turk J Hematol* 23:209–211
 18. Yanagimoto M, Usuki K, Iijima K et al (2003) Simultaneous occurrence of acute myeloid leukemia with multilineage dysplasia and multiple myeloma. *Rinsho Ketsueki* 44:19–24
 19. Osserman E (1967) The association between plasmacytic and monocytic dyscrasia in man: clinical and biochemical studies. In: Killander J (ed) *Gamma Globulins: structure and control of biosynthesis*. Interscience Publishers, New York, pp 578–583
 20. Kim D, Kwok B, Steinberg A (2010) Simultaneous acute myeloid leukemia and multiple myeloma successfully treated with allogeneic stem cell transplantation. *South Med J* 103:1246–1249