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The 6th World Congress on

CONTROVERSIES IN MULTIPLE MYELOMA (COMy)

Chronic neutrophilic leukemia, a rare and challenging diagnosis when associated to myeloma.

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INTRODUCTION

Chronic neutrophilic leukemia (CNL) is a rare BCR-ABL1 negative myeloproliferative neoplasm with often aggressive evolution without stem cell transplantation (SCT). The association with plasma cell dyscrasia has been reported, but relationship remains unclear.

CASE REPORT

A 68-year-old women with monoclonal gammopathy with lambda expression and no clinical symptoms develops isolated neutrophilia over 45x10^9/L.

PET scanner is normal. BCR-ABL, JAK2, FIP1L1, PDGFRα and β, FGFR1, CSF3R are negative, FISH shows duplication 1q, and NGS reveals no clonal mutation. Bone marrow biopsy reveals 10,5% of clonal plasma cells corresponding to myeloma but also hypercellularity > 90% with expanded neutrophilic granulopoiesis. The latter, associated with persisting neutrophilia leads to CNL diagnosis according to WHO 2016.

Hydroxyurea is started and SCT is considered, but not done because of slow evolution. After 14 months of follow-up, PET scanner shows bones evolution and VRd (bortezomib, lenalidomide and dexamethasone) is started.

	Normal values	Diagnosis	1 year from diagnosis	After 2 cycles of VRd
Hemoglobin (g/dL)	12,5-16	14	14,5	12,4
WBC (x10^3/µL)	3,8-11	52,82	41,00	15,13
Neutrophilia	1,4-7,7	**46,01**	**36,90**	**10,97**
Lymphocytes	1-4,8	4,64	2,74	2,28
Monocytes	0,15-1,0	1,42	1,10	1,25
Eosinophilia	0,02-0,58	0,37	0,00	0,26
Basophilia	0,0-0,11	0,00	0,00	0,07
Platelets (x10^3/µL)	150-445	232	247	320
Immunoglobuline(mg/dL)				
IgG	700-1600	1781	2002	1243
IgA	70-400	63	81	66
IgM	40-230	48	63	54
Monoclonal protein		1280	1669	787

ILLUSTRATIONS

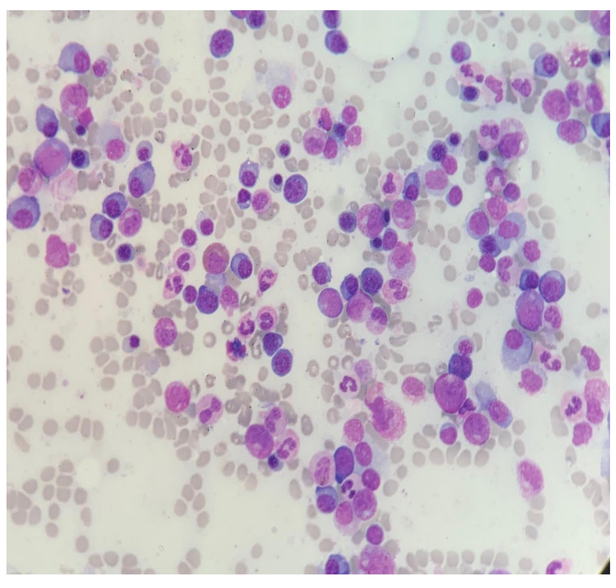

Figure 1. Bone marrow cytology showing numerous plasma cells (>10%) (multiple myeloma) and a large amount of neutrophils (>30%).

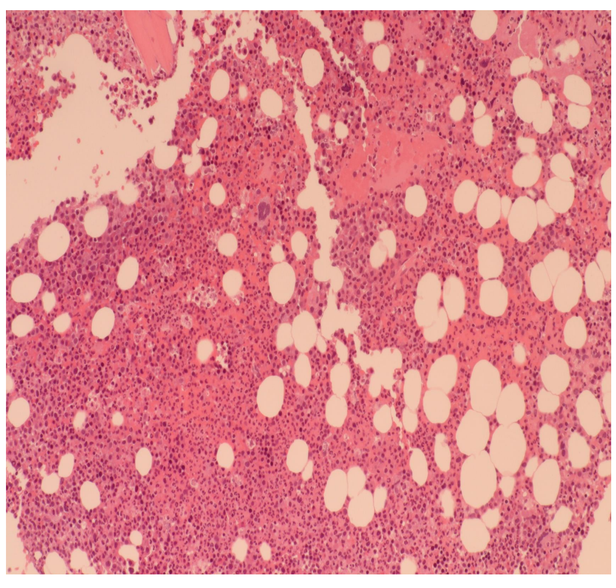

Figure 2. Histology (hematoxylin eosin) showing an hypercellular bone marrow with infiltrating multiple myeloma.

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World Health Organization (WHO 2016) criteria for Chronic Neutrophilic Leukemia

Peripheral blood leukocytosis ≥ 25 x10^9/L
- Segmented neutrophils plus band forms ≥ 80% of white blood cell (WBC)
- Neutrophil precursors (promyelocytes, myelocytes and metamyelocytes) <10% of WBC
- Myeloblasts rarely observed
- Monocyte count < 1 x10^9/L
- No dysgranulopoiesis

Hypercellular Bone Marrow
- Neutrophil granulocytes increased in percentage and number
- Normal neutrophil maturation
- Myeloblasts <5% of nucleated cells

Not meeting WHO criteria for BCR-ABL1 chronic myeloid leukemia, polycythemia vera, essential thrombocytemia or primary myelofibrosis.

No rearrangement of PDGFRα, PDGFRβ or FGFR1 or PCM1-JAK2

Presence of CSF3RT6181 or other activating CSF3R mutation
Or
In the absence of CSF3R mutation, persistent neutrophilia, splenomegaly and no identifiable cause of reactive neutrophilia including absence of a plasma cell neoplasm or if present, demonstration of clonality of myeloid cells by cytogenetic or moleculor studies.

DISCUSSION

A particularly high number of CNL cases is associated with plasma cell dyscrasia, mostly preceding myeloma but few cases had been described simultaneously. Distinguishing CNL from a leukemoid reaction may be challenging. It is now accepted that neutrophilic expansion represents an associated myeloproliferative disease rather than usual reactive and infiltrative leukemoid response to the plasma cell population.

It is currently not clear whether CNL and plasma disorder are clonally related or whether neutrophilia occurs secondarily. Both clonal and non-clonal neutrophilia with plasma dyscrasia have been reported. This identification is not routinely performed in our academic centers and therefore, definitive diagnosis of CNL and adequate treatment requires carefulness. Experience shows that prognostically, myeloma associated CNL may be related to longer life expectancy.

CONCLUSION

Future, particularly clonality research, should help to better understand the uncertain status of myeloid clonality in myeloma and the relationship between plasma cell dyscrasia and CNL, and guide us with the adequate treatment strategy.

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