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23 **Short Running Title:** Synchronous mantle cell lymphoma and Plasma cell dyscrasia

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26 submission.

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34

35 **ABSTRACT**

36

37 **Introduction**

38 Coexistence of NHL with plasmacytoma or multiple myeloma (MM) at same
39 anatomical location is reported only as a few case reports [1].

40

41 **Case report**

42 We report a case of 63-year-old gentleman who presented with nasal obstruction
43 and bilateral cervical and right axillary lymphadenopathy of three months duration.
44 Biopsy from nasal mass revealed diffuse infiltration by atypical lymphoid cells which
45 expressed LCA, CD20, CD5 and cyclin D1 on immunohistochemistry. A diagnosis of
46 extranodal Mantle cell lymphoma was rendered. A staging bone marrow aspirate
47 revealed an increase in atypical lymphoid cells and morphologically atypical plasma
48 cells, consisting 15% and 20% of the nucleated non-erythroid cells respectively. The
49 bone marrow biopsy showed small paratrabecular and interstitial nodular aggregates
50 of atypical lymphoid cells which were highlighted by CD20, CD5 and cyclin D1. In
51 addition, CD138 highlighted an interstitial increase in plasma cells which also
52 demonstrated an aberrant expression of CD56 and cyclin D1. This proved the
53 coexistence of Mantle cell lymphoma and Plasma cell dyscrasia, which is worth
54 reporting.

55

56 **Conclusion**

57 This study clearly demonstrates the unique existence of MCL with plasma cell
58 dyscrasia based on careful morphologic evaluation & a panel of immunostains . A
59 molecular approach to analyze the clonal relationship between the two populations is
60 needed to exclude a composite lymphoma and allow for appropriate treatment.

61

62 **Keyword:** cyclin D1, mantle cell lymphoma, plasma cell dyscrasia, synchronous

63 **TITLE:** Synchronous presentation of Mantle cell lymphoma and Plasma cell
64 dyscrasia: a very rare case report

65

66 **INTRODUCTION**

67 Clonal plasma cell component is well described in some Non Hodgkin lymphomas
68 (NHL), including marginal zone lymphomas (MZL) and lymphoplasmacytic
69 lymphoma (LPL) [2-3]. It is very rarely seen in other NHL like chronic lymphocytic
70 leukemia (CLL), follicular lymphoma (FL) and mantle cell lymphoma (MCL) [1,2,4].
71 Coexistence of NHL with plasmacytoma or multiple myeloma (MM) at same
72 anatomical location is reported only as a few case reports [2,5]. Occasional case
73 report also mentions metachronous presentation of MCL in a case of MM [6]. Herein
74 we report a case of MCL with plasma cell dyscrasia (PCD), on bone marrow in a 65-
75 year-old man.

76

77 **CASE REPORT**

78 A 65-year-old gentleman complained of neck swelling since last six months,
79 underwent cervical lymph node fine needle aspiration (FNA) which revealed
80 granulomatous lymphadenitis. Based on this, he was treated with antitubercular
81 treatment (ATT) at his local place for three months. Due to persistence of cervical
82 swelling and nasal obstruction, he was referred to our institute. On examination, he
83 had bilateral cervical and axillary lymphadenopathy without hepato-splenomegaly.
84 His complete blood counts (CBC) revealed anemia (hemoglobin: 8 gm/dl) with
85 normal total leukocyte ($7.3 \times 10^9/L$) and platelet count ($372 \times 10^9/L$). Liver and renal
86 function tests were normal. Serum LDH (232U/l; normal range: 100-180U/L) and $\beta 2$
87 microglobulin (9.85 mg/L; normal range: 0.83-1.15mg/L) were elevated. Computed
88 tomography (CT) scan of paranasal sinuses showed large lobulated homogenously
89 enhancing soft tissue density in the nasopharynx and right upper oropharynx,
90 extending across the midline upto the posterior choana and left soft palate. It also
91 revealed multiple soft tissue densities in bilateral orbits. Ultrasonography (USG) of
92 abdomen and pelvis revealed mesenteric, peripancreatic and paraaortic
93 lymphadenopathy. A nasal mass biopsy was performed which showed diffuse
94 infiltration by atypical lymphoid cells expressing LCA, CD20, CD5 and cyclin D1.

95 Mib1 proliferation index was 40%. A diagnosis of Extranodal Mantle cell lymphoma
96 was rendered. A staging bone marrow aspirate (BMA) and biopsy (Figure 1)
97 revealed mildly hypercellular particles with trilineage hematopoiesis. Few atypical
98 lymphocytes were seen along with an increase in morphologically abnormal plasma
99 cells. Nucleated non-erythroid cell count done on BMA showed 20% abnormal
100 plasma cells and 15% atypical lymphocytes. Background red blood cells (RBC) did
101 not show any rouleaux formation. Plasma cells showed ballooning of cytoplasm with
102 intracytoplasmic grayish blue inclusions (? immunoglobulin collection) and an
103 eccentric nucleus (Figure 2A). Occasional binucleated cells were also noted. BM
104 sample was not sent for immunophenotyping by flow cytometry (FCM) and thus
105 atypical lymphoid cells were not characterized on aspirate. The BM biopsy showed
106 small paratrabecular and interstitial nodular aggregates of atypical lymphoid cells as
107 well as an interstitial increase in plasma cells (Figure 1A). On immunohistochemistry
108 (IHC), aggregates of lymphoid cells were highlighted by CD20, CD5 and cyclin D1
109 (Figure 1-B, C, D). On careful examination, cyclin D1 was also positive in plasma
110 cells (Figure 2D). These plasma cells were highlighted with CD138, CD56 and
111 showed lambda light chain restriction (Figure 2-B, C). Aberrant CD56 expression
112 proved the neoplastic nature and lambda light chain restriction (Figure 2-E) proved
113 the clonal nature of plasma cell component in this case. MCL component did not
114 reveal either lambda or kappa light chain restriction (Figure 2F). Additional work up
115 for plasma cell dyscrasia was done. Skeletal survey did not reveal any lytic lesions.
116 Serum globulin levels (3.8g/dl) were within normal range (2.8 to 4.3 g/dl). Serum
117 electrophoresis and immunoprotein studies were not performed. The final diagnosis
118 of Mantle cell lymphoma with Plasma cell dyscrasia was offered. Patient was staged
119 IV BEx (Ann Arbor staging for NHL) and started on R-CEOP (Rituximab,
120 Cyclophosphamide, Vincristine, Prednisolone) protocol. On his recent follow up after
121 three months, he is clinically stable; however there is persistent anemia with
122 hemoglobin of 8.4 gm/dl.

123

124 DISCUSSION

125 Co-existence of Mantle cell lymphoma and plasma cell dyscrasia involving the bone
126 marrow is a very rare occurrence. The index case showed presence of extra-nodal

127 mantle cell lymphoma involving nasopharynx without the plasma cell component at
128 that site. However, both the components in the bone marrow were morphologically
129 and immunohistochemically distinct. Morphologically abnormal plasma cells with
130 ballooning of cytoplasm and aberrant expression of cyclin D1 and CD56 alongwith
131 lambda light chain restriction clinched the neoplastic and clonal nature of plasma
132 cells. Though the presence of cyclin D1 both in MCL and plasma cells does not
133 prove their different clonal nature, the expression of CD56 only in plasma cells
134 proves their neoplastic nature and supports the distinct nature of synchronous
135 neoplasms as against the clonal differentiation of MCL with clonal plasma cell
136 differentiation. Unfortunately, BM aspirate was not submitted for cytogenetic studies
137 in index case.

138 Very few cases of MCL with plasmacytoma have been reported in literature
139 previously [1, 5]. These patients were usually more than 60 years of age, with upper
140 respiratory tract being the commonest site of involvement as in the index case [1, 3,
141 5].

142 MCL with clonal plasma cell differentiation/component, within the same tissue
143 biopsies, however has been described in very few studies [2,7]. Young et al reported
144 a case of a nodal MCL with clonal plasma cell differentiation based on kappa- light
145 chain restriction only in plasma cell component and not in MCL, similar to index case
146 [2]. However, in his study demonstration of t(11;14) by FISH (fluorescent in situ
147 hybridization) in both the components suggested that the clonal plasma cells are a
148 part of MCL rather than a second lymphoproliferative disease [2]. Composite
149 presentation of immunophenotypically distinct MCL and extramedullary
150 plasmacytoma in a single anatomical site without plasma cell component in BM has
151 been reported in literature as few case studies [1, 5]. It is important to evaluate this
152 plasma cell component for clonality and also its neoplastic nature using a wide range
153 of IHC panel. Demonstration of cyclin D1 in both MCL and PCD may prove the clonal
154 nature of the disease but not the neoplastic nature of plasma cells. Expression of
155 cyclin D1 is always aberrant in hematolymphoid neoplasms, including MCL, multiple
156 myeloma (MM) and hairy cell leukemia (weak expression) [3,6,8]. Almost 100%
157 cases of MCL express cyclin D1 (cyclin D1 negative MCL-very rare) and cyclin D1
158 positivity correlates with t(11;14) [6,9]. However, only 3-50% cases of MM show

159 cyclin D1 expression and this is associated either with t(11;14) in 3-14% [3] or with
160 extra copies of chromosome 11 in 16% [3,6]. CD56 expression defines the
161 neoplastic nature of plasma cells as against normal plasma cells and is aberrantly
162 expressed in 67-79% cases of plasma cell myeloma [3]. However, unlike in the index
163 case, none of the studies in the literature discussing the coexistence of MCL and
164 plasmacytoma have used CD56 by immunohistochemistry (IHC) to demonstrate the
165 neoplastic nature of plasma cells [1, 2, 5, 7]. In the index case, ballooning of plasma
166 cells on morphology suggested intracytoplasmic accumulation of immunoglobulins,
167 which was confirmed by IHC and it indicated the non-secretory nature of MM which
168 was further reinforced by the normal globulin levels. However serum electrophoresis
169 to demonstrate the 'M' band was lacking in the index case.

170 PCD being an incidental and asymptomatic finding in this case, the primary aim of
171 treatment was chemotherapy for MCL. However, there are certain drugs like
172 bortezomib (proteasome inhibitor), linalidomide/thalidomide (immunomodulating
173 drugs) which have a proven action in both MCL and PCD individually and thus may
174 be used for such rare coexistence [6].

175

176 CONCLUSION

177 In conclusion, our study clearly demonstrates the unique existence of MCL with
178 plasma cell dyscrasia based on careful morphologic evaluation & a panel of
179 immunostains . A molecular approach to analyze the clonal relationship between the
180 two populations is needed to exclude a composite lymphoma and allow for
181 appropriate treatment. At present time, an array of genetic and molecular
182 investigations is under way to explain the relationship between the presence of
183 t(11;14)(q13;q32) and the origin of various hematologic neoplasms. We believe that
184 the present case might offer additional insights to this fascinating topic of composite
185 neoplasms which in turn may yield new avenues for both MCL and myeloma
186 therapy.

187

188 CONFLICT OF INTEREST

189 None

190

191 **AUTHOR'S CONTRIBUTIONS**

192 Komal S Galani

193 Group1 - Acquisition of data

194 Group 2 - Drafting the article, Critical revision of the article

195 Group 3 - Final approval of the version to be published

196

197 Vijaya S Gadage

198 Group1 - Conception and design, Analysis and interpretation of data

199 Group 2 - Drafting the article

200 Group 3 - Final approval of the version to be published

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202 Mahesh K Deshmukh

203 Group1 - Analysis and interpretation of data

204 Group 2 - Critical revision of the article

205 Group 3 - Final approval of the version to be published

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207 Santosh Menon

208 Group1 - Analysis and interpretation of data

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210 Group 3 - Final approval of the version to be published

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212 Sumeet Gujral

213 Group1 - Acquisition of data, Analysis and interpretation of data

214 Group 2 - Critical revision of the article

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216

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248 FIGURE LEGENDS

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250 Figure 1: (A) Bone marrow biopsy showing paratrabecular lymphoid cell aggregates
251 with interstitial increase in plasma cells (H&E); (B) CD20, (C) CD5, (D) cyclin D1
252 highlights paratrabecular lymphoid cell aggregates of Mantle cell lymphoma

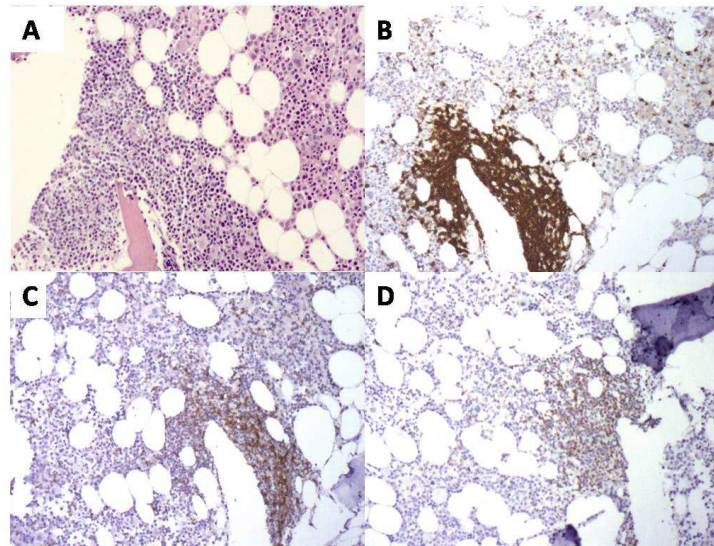
253

254 Figure 2: (A) Plasma cell showing intracytoplasmic collection of immunoglobulins on
255 bone marrow aspirate; B to F: Bone marrow biopsy IHC: (B) CD138, (C) CD56, (D)
256 Cyclin D1 highlights neoplastic plasma cells; lambda light restriction is seen in
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259 FIGURES

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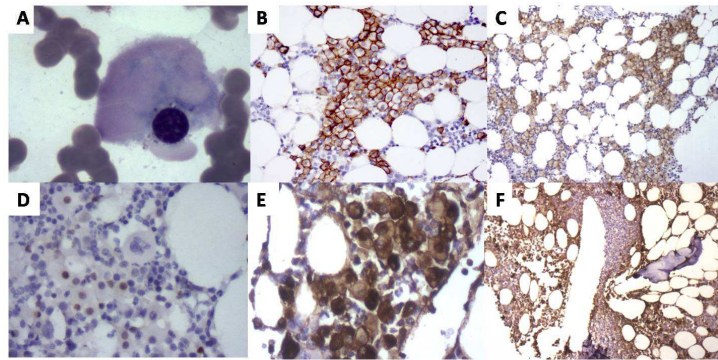
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