J Clin Exp Hematopathol
Vol. 49, No. 1, May 2009

Letter to the Editor

Cyclin D1 Protein Overexpression in Extramedullary Plasmacytoma : A Clinicopathologic Study of 11 Cases

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Keywords: extramedullary plasmacytoma, cyclin D1, fluoresence *in situ* hybridization, immunohistochemistry

To the Editor

To clarify the presence or absence of cyclin D1 overexpression in extramedullary plasmacytomas (EMPs) , we examined 11 cases using an immunohistochemical study. None of the 11 cases showed evidence of underlying multiple myeloma at the diagnosis of EMP.[1]

The main clinicopathological findings of the 11 cases are summarized in Table I. Four (Nos. 1-4) of the 11 cases demonstrated greater than 30% Cyclin $D1^+$ tumor cells (Fig. 1a), whereas there were no cyclin $D1^+$ tumor cells in the remaining seven cases (Nos. 5-11). According to WHO classification standards,[1] two of the four cyclin $D1^+$ cases were poorly differentiated EMP and the other two samples comprised cases of well differentiated EMP and moderately differentiated EMP. Five of the seven cyclin $D1^-$ cases were well differentiated EMP and two were moderately differentiated EMP. Two cases (Nos. 6 and 11) showed prominent amyloid deposition.

Immunohistochemistry was performed on paraffin sections using a Ventana automated (BenchMarkTM) stainer. There were no $CD5^+$ or $CD20^+$ tumor cells in any of the 11 cases. All 11 cases showed monotypic intracytoplasmic immunoglobulins and expressed CD38 and CD138 antigens. The plasma cells exhibited monotypic intracytoplasmic κ light chain in five patients (Nos. 1, 2, 4, 8, and 9) and λ light chain in six (Nos. 3, 5-7, 10, and 11). Intracytoplasmic immunoglobulin heavy chains were positive in nine (Nos. 2-4, and 6-11) of the 10 lesions tested (Nos. 1-4, and 6-11) : of these, four (Nos. 3, 6, 7, and 10) stained positive for IgG, three (Nos. 4, 8, and 9) staind for IgG and IgA, and two (Nos. 2 and 11) stained for IgA alone. IgM were not detected in any of the lesions. There were no $CD56^+$ or human-herpes virus type-8^+ tumor cells in any of the 11 cases.

A two-color fluoresence *in situ* hybridization (FISH) assay using commercially available 14q32 and 11q13 probes (Vysis Inc, Downers Grove, IL, USA) disclosed separate BCL1 and IgH signals in the nuclei of tumor cells, which is a pattern seen in non-rearranged cells (Fig. 1b).[2] However, two (Nos. 2 and 3) of the three cases (Nos. 1-3) were scored as having an 11q13 trisomy or polysomy (Fig. 1c). In the remaining one case (No. 4), there were insufficient materials available for FISH analysis.

Among the four cyclin $D1^+$ cases, one case (No. 1) showed only partial remission and bone marrow involvement was found 13 months after the onset of disease. Complete remission was obtained in the remaining three cases (Nos. 2-4). However, all of the three cases were relapsed (bone marrow = 2, duodenum = 1). Three (Nos. 1-3) of the four cyclin $D1^+$ cases died of disease. Complete remission was achieved in all seven cyclin $D1^-$ cases. Three cases (Nos. 6, 9, and 11) relapsed. The remaining one (No. 11) died due to ovarian cancer.

EMPs are rare, typically solitary tumors lacking any signs of systemic spread, and represent approximately 4% of all

Received : February 18, 2008
Revised : May 12, 2008
Accepted : June 5, 2008
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Table 1. Main clinicopathologic findings of 11 cases

Case	Age/ Sex	Site of disease	Initial therapy	Course of disease	Histology	cIg
1*	52/M	Neck LN	RT + Chem	PR, 13 mon, bone metastasis 34 mon, D (+)	Poorly	κ/-
2*	64/M	Left tonsil, Neck LN	RT	CR, 6 mon, duodenum relapse 15 mon, D (+)	Poorly	κ/IgA
3*	69/M	Right neck, Soft tissue	RT	CR, 6 mon, vertebra relapse 15 mon, D (+)	Well	λ/IgG
4*	82/M	Right larynx	Ope	CR, 60 mon, sternum relapse	Moderately	κ/IgG, IgA
5	47/F	Left nasal cavity	RT	CR, 62 mon, A (-)	Well	λ/NE
6	56/M	Right pharynx	Ope	CR, 96 mon, right neck mass relapse, A (+)	Well**	λ/IgG
7	58/M	Left epipharynx	RT	CR, 76 mon, A (-)	Well	λ/IgG
8	62/M	Right gingiva, Right testis	Ope + Chem + RT	CR, 36 mon, A (-)	Moderately	κ/IgG, IgA
9	62/M	Left maxillary sinus, Neck LN	Ope + Chem	CR, 15 mon, right hemoral bone relapse	Moderately	κ/IgG, IgA
10	67/M	Right paranasal sinus	RT	CR, 45 mon, A (-)	Well	λ/IgG
11	79/F	Left lower leg	Ope	CR, 54 mon, left lower leg relapse & resection 79 mon, D (-) (ovarial cancer)	Well**	λ/IgA

LN, lymph node ; RT, radiotherapy ; Chem, combination chemotherapy ; Ope, operation ; PR, partial remission ; CR, complete remission ; A, alive ; D, dead ; (-), without disease ; (+), with disease ; cIg, cytoplasmic immunoglobuline ; NE, not examined
*, Cyclin D1$^+$; **, associated with amyloid tumor

plasma cell neoplasms.[1] Recently, because of the predominant localization of EMP at mucosal sites, some authors speculated that EMP represents a mucosa-associated lymphoid tissue (MALT) type of lymphoma with extreme plasma cell differentiation.[3] However, all of our 11 cases under evaluation were completely negative for CD20 and lacked lymphoepithelial lesions and/or reactive follicles, which are characteristic histological findings seen in MALT type lymphomas.[1,3]

The cell cycle protein cyclin D1 is overexpressed in about 25-30% of multiple myeloma (MM) cases, most frequently as a result of a t(11;14)(q13;q32) translocation, but also due to other mechanisms.[1,2,4-7] However, little is known about the overexpression of cyclin D1 among EMPs.[4,8]

We found overexpression of cyclin D1 in four (37%) of the 11 EMPs. Compared with cyclin D1$^-$ EMPs, these four cases appears to have characteristic clinicopathological findings such as (i) low-frequency of well differentiated morphology (1/4) ; (ii) high frequency of recurrence (3/3) ; (iii) high frequency of bone marrow involvement during the course of disease (3/4) ; and (iv) an aggressive clinical course.

Although there was no t(11;14)(q13;q32) in any of the three cases examined, FISH analysis demonstrated an 11q13 trisomy or polysomy in two cases, which is similar to multiple myeloma.[1,2,5,7] However, there were no CD56$^+$ tumor cells in any of the four cases.[6]

Cyclin D1 expression in multiple myeloma appears to be associated with a favorable prognosis.[2,7] In contrast to multiple myeloma, the present four cases suggested that Cyclin D1 expression in EMPs appears to be associated with unfavorable prognosis. However, the number of cases was too small to clarify the clinicopathological, immunophenotypic and genotypic findings of Cyclin D1$^+$ EMPs.

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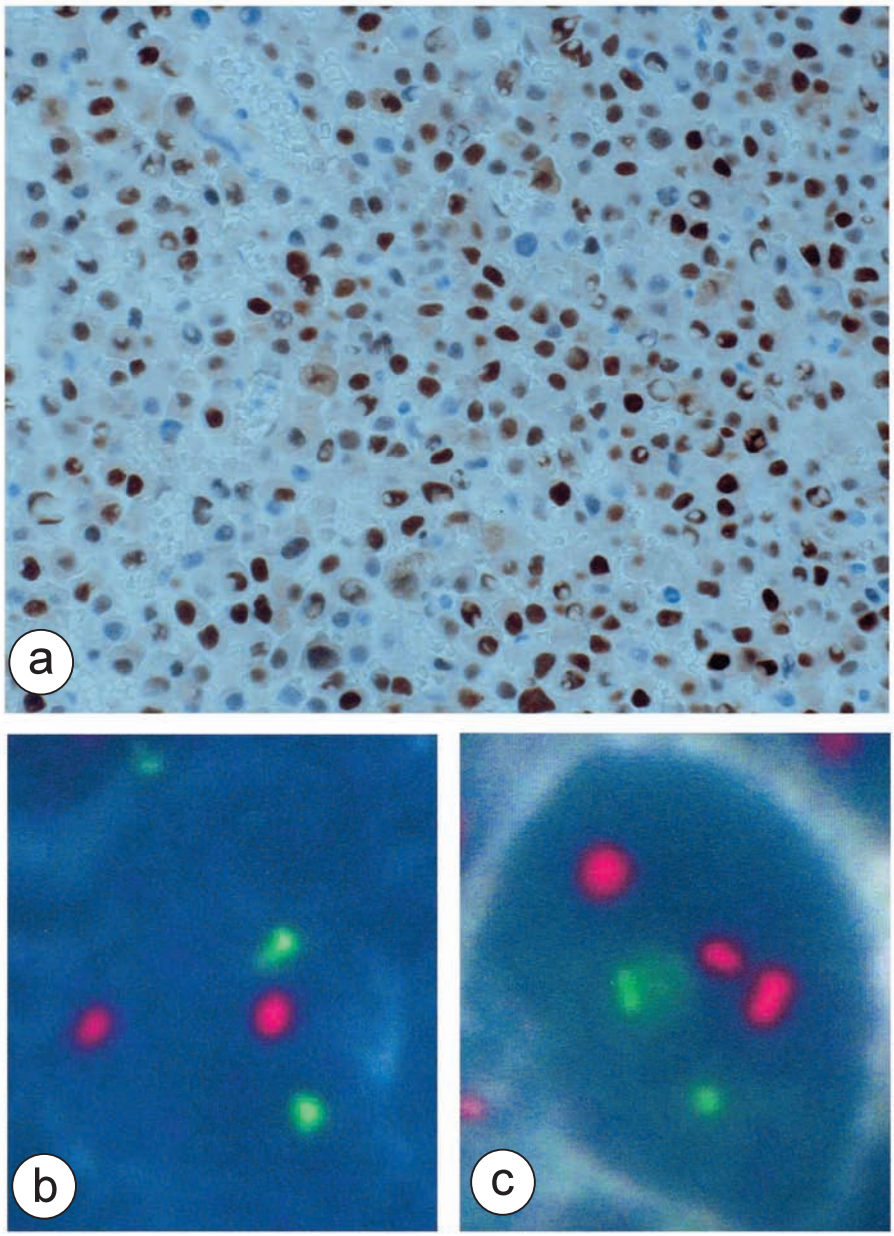

Fig. 1. Morphological characteristsics. (***1a***) Cyclin D1 immunostain demonstrated strong nuclear positivity in more than 50% of the tumor cells. Case 4. x40. Fluorescence *in situ* hybridization analysis for t(11;14)(q13;q32) in extramedullary plasmacytoma. (***1b***) In normal cells, two red signals (*BCL-1*) and two green signals (*IgH*) were observed. (***1c***) A gain of BCL-1 was identified as three red *BCL-1* signals.

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