

Plasma cell leukemia producing monoclonal immunoglobulin E

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Abstract A 78-year-old male with lumbar pain and dim consciousness presented the clinical pictures of plasma cell leukemia (PCL) producing a large amount of monoclonal immunoglobulin E (IgE)/kappa protein. Laboratory investigation demonstrated an elevated serum calcium level and renal dysfunction. Systemic bone X-ray survey disclosed only a solitary osteolytic lesion. Circulating plasma cells demonstrated CD19⁺/CD56⁺ and MPC-1⁺/CD49e⁺/CD45⁺, the latter indicating the immature phenotype of the tumor cells. Bone marrow was occupied with immature, atypical plasma cells, of which cytoplasm was positive for IgE by direct immunofluorescence analysis. Chromosomes revealed a translocation of (11;14)(q13;q32), which is

concordant with cyclinD1-protein overexpression by immunohistochemistry. He was treated with dexamethasone and vincristine, which somewhat improved the laboratory findings. He died of tumor progression after 4-month admission. The clinical and biological characteristics of IgE-producing PCL, a very rare type of plasma cell dyscrasia, are discussed, reviewing the past literature.

Keywords Plasma cell leukemia · Immunoglobulin E (IgE) · Multiple myeloma · Bone lesion · Cellular adhesion molecules

1 Introduction

Since the first report of a patient with plasma cell dyscrasia (PCD) producing immunoglobulin E (IgE) [1], approximately 44 cases of PCD presenting a significant amount of serum monoclonal IgE have been found in the literature [2, 3]. IgE-producing PCDs are considered to represent less than 0.01% of all types of multiple myeloma (MM)-related diseases [4], and thus fewer than ten patients of plasma cell leukemia (PCL) with IgE secretion have been reported [5]. Clinical and pathological features of IgE PCDs have not been sufficiently analyzed because of a small number of such patients. We herein report a patient with primary PCL producing a large amount of monoclonal IgE and discuss the biological characteristics, including immunophenotypes and cytogenetics, of this rare type of PCD, while reviewing the literature.

2 Case report

A 78-year-old male was admitted to the Saku Central Hospital because of lumbar pain and drowsiness, which

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were manifested a month ago. He had neither serious diseases in his past history nor apparent aberration in laboratory test findings on occasional health examinations before the symptoms began. On physical examination, he was somnolent and had percussion pain at his sternum bone. His skin was dry and his heart rate was 68/min with a supraventricular arrhythmia. He was anemic but showed no jaundice. Liver, spleen and lymph nodes were not palpable.

Initial laboratory investigation disclosed a white blood-cell count of $21.3 \times 10^9/L$, of which 31% were immature atypical plasma cells, a hemoglobin of 86 g/L, and a thrombocytopenia (platelet count; $81 \times 10^9/L$). The peripheral blood smear showed a rouleaux formation. The erythrocyte sedimentation rate was 106 mm/h. Total protein was 83 g/L with prominent hypergammaglobulinemia (48.1% of the total serum protein) constituting a large monoclonal spike, which was identified as IgE/ κ protein by immunoelectrophoresis (Fig. 1). The amounts of other serum immunoglobulins were obviously decreased (188, 14 and 7 mg/dL for IgG, IgA and IgM, respectively).

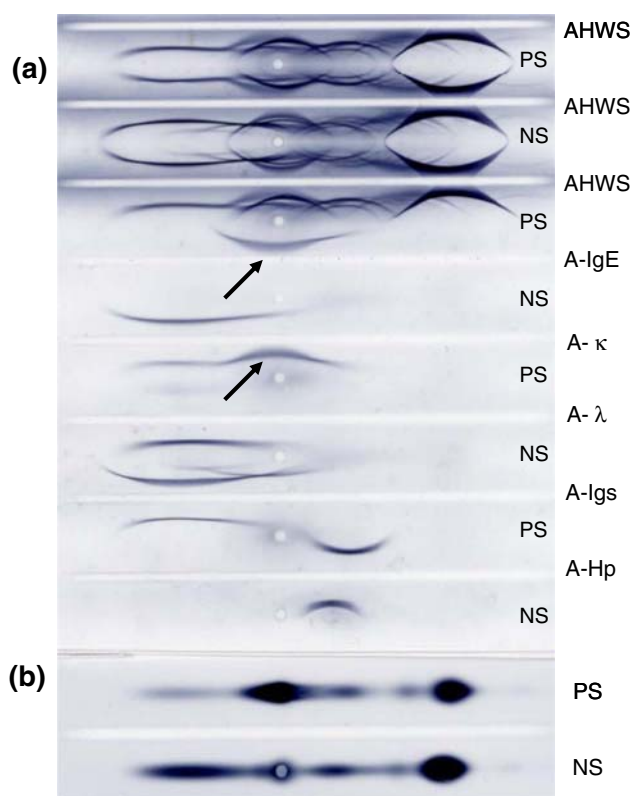


Fig. 1 Immunoelectrophoretic (a) and electrophoretic (b) patterns of the patient's serum. Immunoelectrophoretic patterns obtained with antisera to human whole serum (AHWS), ϵ -chain (A-IgE), κ light chain (A- κ), λ light chain (A- λ), immunoglobulin G, A and M (A-Igs), and haptoglobin (A-Hp) (A). The arrow indicates an abnormal precipitin arc of IgE/ κ type monoclonal protein. The patient's serum was also tested and found negative for IgD (not shown in the figure). PS patient serum, NS normal serum. Anode is to the right

IgD was below the detection limit. IgE was quantitated as 38 g/L, which was greater than his serum albumin concentration. Bence Jones protein was negative even in the $50\times$ concentrated urine. The blood urea nitrogen level was 41 mg/dL, creatinine of 3.1 mg/dL and uric acid of 10.9 mg/dL. The serum calcium level was 12.8 mg/dL, which caused his dim consciousness. β_2 -Microglobulin was markedly increased in both the serum (21.1 mg/L) and the urine (2.36 mg/L). Plasma viscosity was within normal limits. Chest X-ray revealed a cardiomegaly and the congestion in both lung fields. A systemic bone X-ray survey disclosed a solitary osteolytic lesion in his right humerus. Spondylitic changes and compression fractures were observed in his cervical, thoracic and lumbar vertebrae. In addition, tumor-cell infiltration was suspected in his lumbar vertebrae by the MRI examination.

Bone marrow was slightly hyperplastic and occupied with immature, atypical plasma cells (Fig. 2), of which the cytoplasm was positive for IgE by a direct immunofluorescence method in various fluorescence intensities (Fig. 3). A flow cytometric analysis for surface antigen expression on the CD38-positive cells demonstrated $CD19^-/CD56^-$ and $MPC-1^-/CD49e^-/CD45^{+/-}$, the latter indicating the immature phenotype of proliferating plasma cells. Approximately 70–80% of the cells expressed CD45 antigen and 30–40% were positive for CD138. The tumor cells curiously expressed CD33, a myeloid antigen. Expressions of CD20, CD58, CD117 and CD79a were negative. CyclinD1, bcl-2 and MUM1 were positive, but CD138 was negative by immunohistochemistry. Ki-67 (MIB1) was expressed in approximately 30–40% of the cells. Chromosome analysis of circulating tumor cells revealed a translocation of (11;14)(q13;q32), which is consistent with the cyclinD1-protein overexpression.

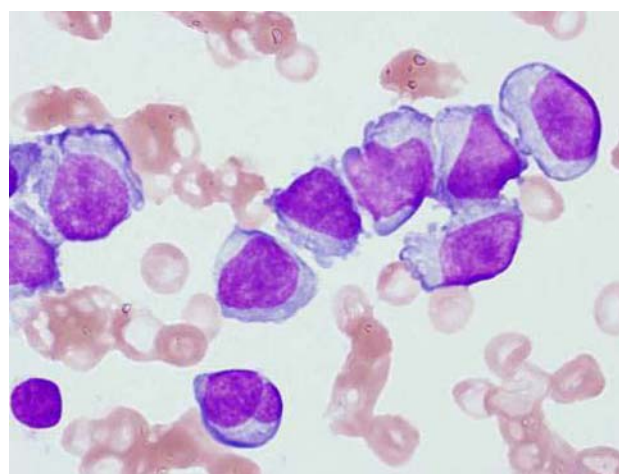


Fig. 2 Bone marrow blood smear from the patient (Wright Giemsa stain, $\times 1000$). Proliferation of immature, atypical plasma cells can be observed. Some cells have multiple nuclei

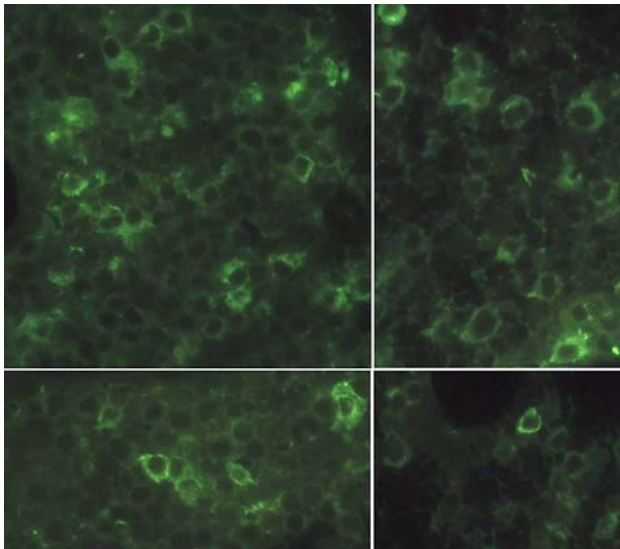


Fig. 3 Direct immunofluorescence analysis stained cells with the FITC-conjugated rabbit anti-human IgE (DakoCytomation, Denmark). Bone marrow blood cells were stained with the anti-IgE antibody in various fluorescence intensities

Southern blotting of the immunoglobulin heavy chain gene demonstrated rearrangement bands.

The patient received intravenous administration of a standard dose of calcitonin preparation immediately after admission and for 2 consecutive days. The serum calcium level was rapidly decreased to the normal range by the 3rd hospital day. Successful reduction of the serum calcium level improved his dim consciousness. Following the two cycles of the chemotherapy (dexamethasone 20 mg/day $\times$ 4 days, vincristine 1.5 mg on day 1), a white blood-cell count decreased to $4.9 \times 10^9/L$, while a platelet count increased to $177 \times 10^9/L$, with few tumor cells appeared in the peripheral blood. The amount of γ -globulin also decreased to 26 g/L (35% reduction). However, 3-week drug-free periods for infection control resulted in the regrowth of the tumor cells in the peripheral blood and the monoclonal protein component again increased. Chemotherapy partially relieved his bony pain, but was discontinued soon because of senile dementia deteriorated during his hospital stay. He died of tumor progression after 4-month admission. Postmortem investigation demonstrated the extensive tumor-cell proliferation and invasion in the bone marrows, liver, spleen and other organs investigated, but there was no evidence for amyloid protein deposition in his organs examined.

3 Discussion

We describe a patient with IgE PCL and analyzed the clinical and pathological features of this rare subtype of

PCD together with cellular intrinsic biology (e.g., immunophenotype and chromosomal aberration), for the latter information was scarcely available in the literature. The circulating plasma cells lacked the CD56 antigen, which has been considered to have an important role in anchoring plasma cells to the bone marrow stroma [6, 7]. Likewise, CD138 and CD58, another adhesion molecules [8, 9], were weakly or negatively expressed on the cells. Immature phenotypes of the neoplastic plasma cells characterized by the MPC-1⁻/CD49e⁻/CD45^{+/+} antigen expressions [10–12] corresponded to the aggressive clinical course of the patient. Chromosome analysis demonstrated a translocation of (11;14)(q13;q32), which was reported as a “hallmark” of some MM variants such as IgE-producing PCD [13]. Indeed, a cryptic t(11;14) was also shown in a cell line established from a patient with IgE MM [14].

PCL itself is a rare presentation of PCD. Its incidence is estimated to be 1–2% of malignant monoclonal gammopathies [15]. There are two forms of PCL: the primary form occurring in patients without preceding MM (de novo presentation in leukemic phase), and the secondary form arising as a terminal manifestation in patients with MM. An aggressive clinical course and no history of prior smoldering PCD suggested that our patient had developed the primary PCL rather than the secondary one. Macro et al. [16] demonstrated a higher incidence of PCL in IgE PCDs than that in other classes of PCDs (approximately 18% vs. 1.5–2%), although the former presents various clinical pictures as well. Including our patient described, we found 8 cases of IgE-producing PCL in the literature (6 primary and 2 possible secondary PCLs [1, 5, 17–21]) (Table 1). Notably, 4 of 6 primary IgE PCL patients had neither osteolytic skeletal lesions nor elevation of serum calcium concentrations. In fact, the lower incidence of lytic bone lesions was reported in patients with IgE PCD than that in patients with PCD from other immunoglobulins than IgE (50 vs. 80%) [16, 22].

Our patient showed an elevated serum calcium level, but we found only a solitary lytic bone lesion on the systemic bone X-ray survey. Other investigators also demonstrated a paradoxical finding, that is, the lower incidence of lytic bone lesions but a higher frequency of hypercalcemia in PCL than those seen in MM [15, 23]. Expression of some cellular adhesion molecules seems to relate to the different incidence and degree of bone involvement between PCL and MM. Plasma cells from patients with PCL frequently lack the CD56 antigen [24], while a majority of MM patients upregulate CD56 [25]. Anchorage of neoplastic plasma cells to the stromal cells induces osteoclast differentiation and activation, enhancing osteoclastic bone resorption and leading to extensive bone destruction [26, 27]. Thus, the lack of CD56 expression appears to affect the bone marrow microenvironment and have negative

Table 1 IgE-producing plasma cell leukemia (PCL) reported in the literature

References	Age/ sex	Primary/ secondary PCL	Light chain	Bence Jones protein	Total protein (g/L)	IgE (g/L)	Hemoglobin (g/L)	Platelet ($\times 10^9/L$)	WBC ($\times 10^9/L$)	Plasma cells in PB (%)	Plasma cells in BM (%)	Renal failure	Hyper- calcemia	Bone lesion	Treatment	Response	Follow-up (months)
Johansson [1]	50/M	Primary	λ	+	95	41.5	102	ND	16	61	ND	-	ND	None	ND	ND	ND
Ogawa [17]	60/M	Primary	λ	+	125	75	40	45	9.5	65	- ^b	+	-	None	MP	PR	8+
Yoshitake [18]	54/M	Secondary	κ	+	110	27	63	135	6.7	27	58	+	+	Osteolytic	MP, CPA	PR	13
Vaerman [19]	55/F	Secondary	κ	Trace	99	46	80	40	2.7–17	0–12	53	+	-	None	MP	NA	13
West [20]	67/M	Primary	λ	+	102.5	38	11	ND	11.8	20	90	+	-	None	M	PR	8
Gallango [21]	38/M	Primary	κ	-	69	16	97	135	17.8	10	40	+	+	Osteolytic	MP	PR	NA
Yamagata [5]	69/F	Primary	κ	+	85	- ^a	97	119	20.7	44	72	-	-	Osteoporosis	VAD, MP, IFN- α	CR	24
Takemura	78/M	Primary	κ	-	83	38	86	81	21.3	31	61	+	+	Osteolytic	VCR, DEX	PR	4

MP melphalan + prednisolone, CPA cyclophosphamide, M melphalan, VAD vincristine + doxorubicin + dexamethasone, INF- α interferon- α , VCR vincristine, DEX dexamethasone, PB peripheral blood, BM bone marrow, ND not described, NA not available, PR partial response, CR complete remission

^a The amount of IgE was expressed as $1,177 \times 10^4$ U/mL (normal limit <400 U/mL) in the literature

^b Described in the literature as: bone marrow aspiration disclosed almost total replacement by plasma cells

effects on local bone destruction in PCL. Indeed, Pellat-Deceunynck et al. [24] demonstrated that in the PCL and MM patients the lack or weak expression of CD56 was associated with a significantly less aggressive osteolytic potential and with a trend for malignant plasma cells to circulate in the peripheral blood more overtly. Recently, some soluble factors (e.g., macrophage inflammatory protein (MIP)-1 α and MIP-1 β [26, 28]) have been identified as the osteoclast-activating factors produced by MM cells. In PCL, malignant plasma cells which do not express cellular adhesion molecules may less contribute to local bone destruction through cell–cell interactions, but expansion of tumor cells producing these soluble factors in peripheral blood may result in the systemic activation of osteoclasts and diffuse bone resorption (and hypercalcemia), with less apparent local lytic bone lesions.

Our patient may represent, at least in part, the biological characteristics of IgE-producing PCL. Further accumulation of the patients will provide information for the intrinsic biology of this rare PCD.

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