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Waldenström's Macroglobulinemia in a 10-year stable IgG Monoclonal Gammopathy of Undetermined Significance

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To the editor

Waldenström's macroglobulinaemia (WM) is a distinct B-cell lymphoproliferative disorder characterized by the infiltration of lymphoplasmacytic cells into bone marrow and the presence of an IgM monoclonal gammopathy [1]. Although patients with biclonal/triclonal gammopathy have been reported to be around 2% in multiple myeloma (MM) or 5-8% in monoclonal gammopathy of Undetermined Significance (MGUS), biclonality in WM has only occasionally been reported [2]. In several previous case reports of biclonal WM, the second clone were mostly non-IgM that appeared in a pre-existing WM [3,4]. However, there is no report of WM that appeared in a pre-existing non-IgM MGUS. Here we report a highly unusual case of WM occurred in a patient with a long-term stable IgG MGUS.

A 74-year-old male atomic bomb survivor underwent M-protein screening in December 1991 at the Nagasaki Atomic Bomb Casualty Council Health Management Center where the M-protein screening test has been offered to over 50,000 subjects since October 1988 [5]. He had already taken the screening test in 1989 and 1990, but no M-protein had been noted. He had a medical history of hypertension. In 1991, however, a small and single peak was detected on the gamma region of globulin in cellulose-acetate electrophoresis (CEP) of serum protein (**Fig. 1**). The immuno-elecrophoreses (IEP) showed a monoclonal IgG-lambda band. The concentration of serum Igs was slightly high in three major isotypes. Other laboratory tests revealed almost normal values and no Bence-Jones (BJ) protein in urine. Physical examination revealed no abnormal finding. He refused to undergo bone marrow aspiration test, then a hematologist at the health management center diagnosed the patient as having IgG-MGUS based on the criteria of serum M-protein less than 3g/dL, no anemia, and no hypercalcemia [2]. The patient was followed annually at the center. The concentration of serum IgG, IgM and IgA decreased gradually and reached the normal range in 1998. However, the serum IEP still revealed a monoclonal IgG-lambda band **(Fig. 1).** From

1991 to 1998, there was no particular change in his physical examination. In December 2000, he visited the center with symptoms of headache, general fatigue, and weight loss. Physical examination revealed generalized lymphadenopathy and hepatosplenomegaly. Serum CEP showed an extremely sharp peak of a single monoclonal protein in the gamma region as same position as before **(Fig. 1).** He was referred to a tertiary hospital. Although serum CEP showed a single peak, the serum IEP showed two monoclonal bands, IgG-lambda and IgM-lambda. The IgM concentration was extremely high (4,785 mg/dl), whereas the serum IgG and IgA were in the normal range. Other laboratory tests revealed the following values: WBC, 5.8 x 10^9 /L (no abnormal cell); hemoglobin, 12.4 g/dl; total serum protein, 8.7 g/dl; LDH, 233 IU/l; serum calcium, 9.1 mg/dl; no protein in urine. Skull Xp and CT showed no osteolytic lesion. He again refused to undergo bone marrow aspiration test. He was diagnosed with WM and followed on an outpatient basis. His generalized lymphadenopathy and hepatosplenomegaly worsened gradually. In May 2001, he underwent bone marrow aspiration and cervical lymph node (LN) biopsy. On bone marrow smears, the infiltration of a mixture of small to medium sizes of lymphoplasmacytic cells was seen **(Fig. 2A)**. In LNs, pathological analyses revealed diffuse infiltration of abnormal medium-sized lymphoid cells **(Fig. 2B and C).** Imunophenotypic characteristics of the malignant cells from LNs by flow cytometry analysis revealed positive for CD19 (61.3%), CD20 (61.3%), s-IgM (58.8%), s-Ig lambda (63.3%), CD22 (46.5%), CD24 (54.4%), HLA-DR (64.8%), and s-IgD (54.7%), weakly positive for CD5 (22.1%), and negative for s-IgG (6.7%), CD23 (8.1%), CD10 (8.9%), CD38 (17.5%), and CD56 (0.5%). These expression patterns were typical for WM rather than other B-cell malignancies [1]. Cytogenetic analysis showed 46XY, inv(16)(p13q13), t(17;18)(q25;q21) in one of 20 metaphases and a normal karyotype in the other cells. There were no abnormal cells in the peripheral blood sample. He was treated with cyclophosphamide, vincristine, and pirarubicin (THP-adriamycin), but no response was observed. He died in December 2001.

The clinical course of this patient was highly unusual and interesting. By taking consideration of impossible class switching from IgG to IgM and no increase of the serum level of IgG in the course, we supposed the WM clone evolved as a new clone

independent from the pre-existing IgG MGUS. *Martín-Jiménez et al.* investigated VDJ rearrangement of biclonal cells from a WM patient who developed an IgG paraprotein 4 years after diagnosis of WM [4]. They found both clones derived from the single clone with the same somatic mutation. *Kriangkum et al.* also investigated VDJ rearrangement of 4 WM patients with biclonal clones at diagnosis [6]. Their two cases with biclonal IgM/IgM isotypes shared identical VDJ rearrangements with mutational profiles but other two cases with different heavy chain isotypes (IgM/IgA and IgM/IgG) showed distinct parent B-cells of the two clones having different VDJ rearrangements and tissue localization in bone marrow. The latter cases could well explain our rare case that WM clone might appear independently from pre-existing IgG MGUS. *Reiman T et al*. reported that some MM patients with clinical isotype of IgG had nonclinical clonotypic IgM in bone marrow [7]. Their report provided another possibility that WM cells in our case might originate from a pre-existing nonclinical B cell clone secreting IgM.

Risk factors for coexistence of oligoclonal clones in paraproteinemia are still unknown. *Zent et al*. reported that around 10% of MM patients that received high-dose chemotherapy had transient oligoclonal bands including IgM or an apparent isotype switch during the recovery of Ig production [8]. However, our patient did not undergo any chemotherapy before the IgM clone appeared. Radiation exposure might be possible as a risk factor for this patient because he was an atomic bomb survivor. However, his exposed-radiation dose was estimated to be zero because he was not in the city at the bombing.

Even recent molecular investigations did not give a clear answer for the origin of IgM-secreting clone that appeared in non-IgM MGUS. The present case might provide an additional consideration for the origin of biclonality in WM.

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Figure legends:

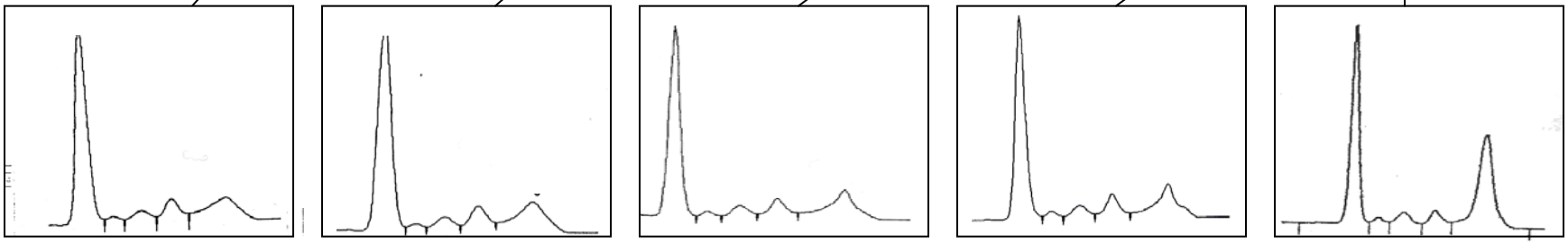
Fig. 1. Clinical course of the patient. The upper table shows concentration changes of serum Igs over time. Normal ranges of Igs were IgG 1109-1726 mg/dl, IgM 135-267 mg/dl, and IgA 160-351 mg/dl. Figures in the middle shows the change of M-peak on cellulose-acetate electrophoresis (CEP) of serum protein at visiting days. The bottom row shows results of immuno-elecrophoreses (IEP).

Fig. 2. Morphological appearance of bone marrow and lymphnode. (A) Bone marrow specimen reveals 4.0% of almost normal plasma cells and 33.6% of small to medium abnormal lymphoid and plasmacytoid cells (May-Grunwald Giemsa stain, original magnification 1000x). (B) Resected lymph node specimens show diffuse infiltration of abnormal medium-sized lymphoid cells (H&E stain, original magnification 100x) and (C) (H&E stain, original magnification 400x).

Fig.1

	Date of examination							
Ig type	'91.02	'92.07	'93.12	'94.12	'96.12	'97.06	'98.12	'00.12
IgG (mg/dL)	2109	2189	1892	2009	2122	1947	1653	1332
IgM (mg/dL)	443	469	206	288	237	246	208	4785
IgA (mg/dL)	496	512	418	456	401	449	308	240

CEP



IEP

'91.02	'92.07	'93.12	'94.12	'96.12	'97.06	'98.12	'00.12
IgG, lamda	IgG, lamda	IgG, lamda	IgG, lamda	IgG, lamda	IgG, lamda	IgG, lamda	IgG, lamda IgM, lamda

Fig.2