

Angioimmunoblastic T-Cell Lymphoma with Coexisting Plasma Cell Myeloma: A Case Report and Review of the Literature

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Angioimmunoblastic T-cell lymphoma (AITL) is recognized as a distinct clinicopathological subtype of peripheral T-cell lymphomas. Its clinical features include generalized lymphadenopathy, constitutional symptoms, and autoimmune-related findings, such as hemolytic anemia. Pathologically, AITL is characterized by a polymorphous infiltrate in lymph nodes with prominent proliferation of high endothelial venules and follicular dendritic cells. We present an 80-year-old Chinese man with generalized lymphadenopathy and pulmonary infection, diagnosed as AITL based on the distinctive pathological findings and T-cell receptor gamma (TCR- γ) gene rearrangement analysis of lymph nodes. Importantly, the patient suffered from a coexisting plasma cell myeloma, as judged by monoclonal immunoglobulin in the serum, immature plasma cells, and rearrangement of the immunoglobulin heavy-chain (IgH) gene in the bone marrow. The patient received two courses of the chemotherapy but died of pneumonia 6 months after diagnosis. AITL can be accompanied by polyclonal or clonal proliferation of B lymphocytes; however, AITL are rarely associated with plasma cell proliferation. In fact, 14 AITL cases with plasma cell proliferation have been reported in the literature, but none of them manifested the infiltration of monoclonal immature plasma cells in the bone marrow. To the best of our knowledge, this is the first report of newly diagnosed, concurrent AITL and plasma cell myeloma, providing the evidence for the interplay between malignant T cells and plasma cell proliferation. A review of the literature has also supported a relationship between AITL and plasma cell proliferation. Awareness of this relationship is important for correct diagnosis and appropriate treatment of AITL.

Keywords: angioimmunoblastic T-cell lymphoma; cytokines; gene rearrangement; myeloma; plasma cell
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Introduction

Angioimmunoblastic T-cell lymphoma (AITL), a unique subtype of peripheral T-cell lymphoma, is a relatively infrequent disease accounting for 15-20% of peripheral T-cell lymphoma and 1-2% of all non-Hodgkin lymphomas (Rudiger et al. 2002). AITL generally occurs in elderly patients and is associated with advanced-stage disease, a variety of immune dysfunctions, and poor prognosis (Dogan et al. 2008). Histopathologically, AITL derives from a unique subset of T cells which are called the follicular helper T (TFH) cells, and displays distinctive features that are characterized by effacement of the lymph node architecture, a paracortical polymorphic infiltrate, the proliferation of arborizing high endothelial venules (HEVs)

and follicular dendritic cells (FDCs), and occasional background expansion of Epstein-Barr virus (EBV)-harboring B immunoblasts (Dogan et al. 2003, 2008; Dunleavy et al. 2007). Recently, several research groups focused on the behavior of plasma cells in AITL, which ranged from reactive plasmacytosis to striking clonal proliferation (Balague et al. 2007; Sakai et al. 2007; Yamane et al. 2007; Ahsanuddin et al. 2011; Huppmann et al. 2013; Nagoshi et al. 2013). However, the role of the plasma cell as a component of the microenvironment in AITL and the functional interaction between plasma cells and tumor cells have not yet been deciphered (Gaulard and de Leval 2014).

Here, we report a case of AITL accompanied by plasma cell myeloma in an 80-year-old man who presented with extensive lymphadenopathy and pulmonary infection.

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To date, only 4 AITL cases (Zettl et al. 2002; Balague et al. 2007; Huppmann et al. 2013) reported in the literature exhibited monoclonal plasma cell proliferation in lymph nodes, but not in the bone marrow. To the best of our knowledge, this is the first report of newly diagnosed concurrent AITL and plasma cell myeloma, showing prominent monoclonal plasmacytosis in the bone marrow.

Case Presentation

An 80-year-old man with a 2-month history of progressive lymphadenopathy, cough, dyspnea and night sweats was referred to our institution. The patient denied a history of fever, pruritus, skin rash, bone pain or weight loss. His medical history was notable for hypertension and chronic bronchitis. His medical record from local hospitals revealed normal complete blood counts, normal urine tests and normal biochemical analysis, including globulin tests, 6 months and one year before admission. At presentation,

generalized enlargement of the lymph nodes in the bilateral mandibular, cervical, supraclavicular, axillary, and inguinal regions was remarkable, with a maximum diameter of about 10 cm (Fig. 1A). No hepatosplenomegaly was noted.

Laboratory studies revealed the following: hemoglobin, 86 g/L; leukocytes, $5.14 \times 10^9/L$, with 89.3% neutrophils and 6% lymphocytes; albumin, 25.4 g/L (normal range, 35-55 g/L); globulin, 56.8 g/L (normal range, 19-34 g/L); lactate dehydrogenase, 330 IU/L (normal range, 110-220 IU/L); C-reactive protein, 38.70 mg/L (normal range, < 5 mg/L); β_2 -microglobulin, 12.90 mg/L (normal range, 0.7-1.80 mg/L); and a positive Coombs direct antiglobulin test. Serum protein electrophoresis revealed a monoclonal protein spike (Fig. 2A). The monoclonal protein was identified as IgA lambda (IgA, 29,800.00 mg/L; normal range, 836-2,900 mg/L) by serum protein immunofixation (Fig. 2B). The serum viral loads of cytomegalovirus and EBV were negative. In addition, computed tomography scans of

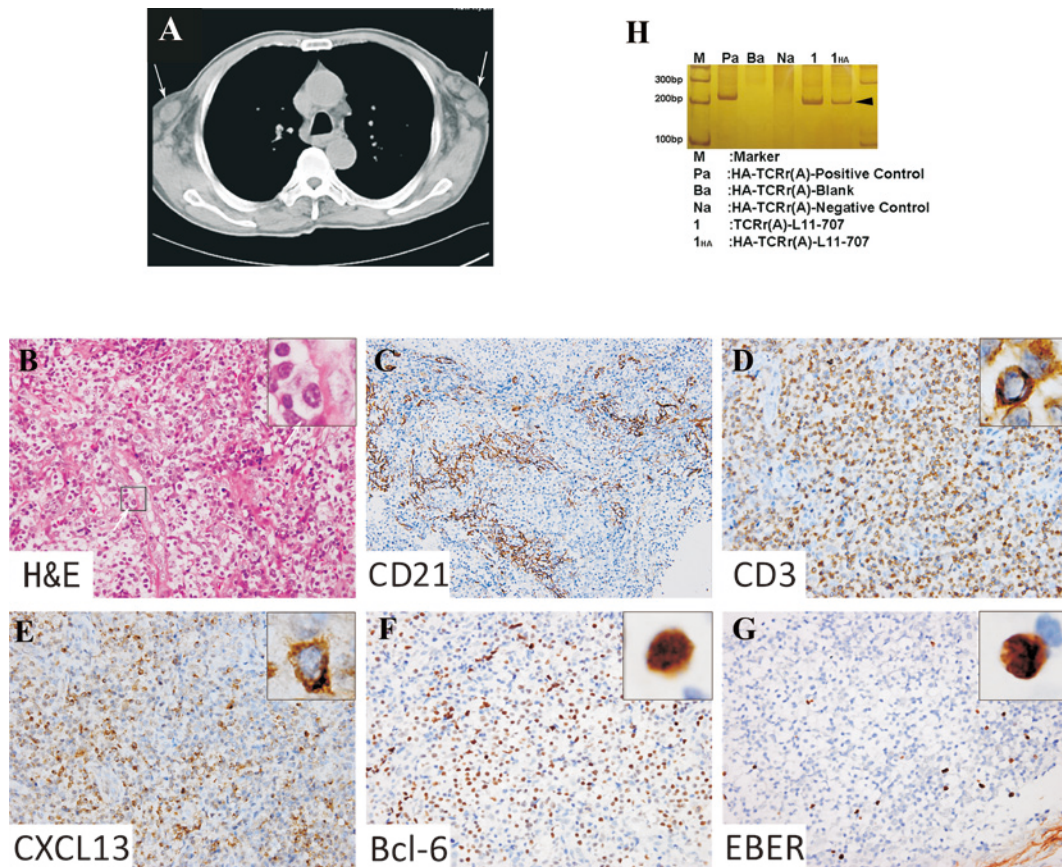


Fig. 1. AITL in the lymph nodes.

A. Computed tomographic image of the chest, showing prominent bilateral axillary lymphadenopathy. B. Hematoxylin and eosin staining reveals histological features of AITL. The lymph node architecture is effaced by a polymorphic infiltrate, with prominent proliferation of arborizing HEVs, and perivascular aggregation of neoplastic clear cells is observed. The arrow indicates a large clear cell with clear or pale cytoplasm that is adjacent to an HEV ($\times 400$, detail in inset). C. Immunostaining of the lymph node using anti-CD21 antibody, highlighting an expanded meshwork of FDCs that wrap around the arborizing vessels ($\times 200$). Immunostaining of the lymph node using anti-CD3 (D), anti-CXCL13 (E) and Bcl-6 (F) antibodies reveals their expression in tumor cells ($\times 400$; insets $\times 1,000$). G. In situ hybridization for EBERs demonstrating positivity in certain scattered cells in the infiltrate ($\times 400$; insets $\times 1,000$). H. Clonality study using the BIOMED-2 TCR gene rearrangement assay. A heteroduplex analysis of a cervical lymph node shows a clonal band in lane 1A (arrows).

the neck, chest, and abdomen revealed polyadenopathy, affecting cervical, supraclavicular, axillary, mediastinal, hilar, para-aortic, retroperitoneal, and inguinal lymph nodes (Fig. 1A) and multifocal patchy opacities in the bilateral lower lung zones, indicating severe infection. A skeletal survey also revealed osteoporosis of the spine and pelvis but no osteolytic lesions.

The patient provided consent for use of his medical record and samples for clinical and research purposes, and the examination was performed in accordance with both the ethics committee of West China Hospital and the Helsinki Declaration. A cervical lymph node biopsy collected at our hospital revealed effaced nodal architecture, marked proliferation of HEVs, and clusters of infiltrating medium-sized lymphocytes with clear cytoplasm (Fig. 1B). CD21-positive FDCs (Fig. 1C) were present. Furthermore, immunohistochemical staining indicated that the clear cells were positive for CD3ε, CD3 (Fig. 1D), CXCL13 (Fig. 1E) and Bcl-6 (Fig. 1F). The Ki-67 index was approximately 50%. Scattered plasma cells were CD20, CD138 and PC positive

but lacked light-chain restriction. A heteroduplex PCR analysis of the rearranged T-cell receptor gamma (TCR-γ) gene and the immunoglobulin heavy-chain (IgH) gene was additionally performed according to the BIOMED-2 protocols to assess clonality (van Dongen et al. 2003). This assessment identified a clonal TCR-γ gene rearrangement (Fig. 1H) but failed to demonstrate IgH clonality. Finally, the distinct lymph node pathological features fit the diagnosis of AITL.

Marrow aspirate smears demonstrated depressed erythropoiesis (erythroid precursors, 17%) and unexpectedly, an increased plasma cell population (31.5%) among all nucleated cells. Plasmablasts, binucleated and multinucleated plasma cells and a rouleaux formation of red blood cells were also easily observed (Fig. 2C). Flow cytometry analysis identified a population of aberrant plasma cells with strong CD38 and CD56 expression, low CD20 expression, and cytoplasmic lambda light-chain restriction (Fig. 2D). In bone marrow trephine biopsy specimens, most of the bone marrow was replaced by diffuse sheet of CD138-

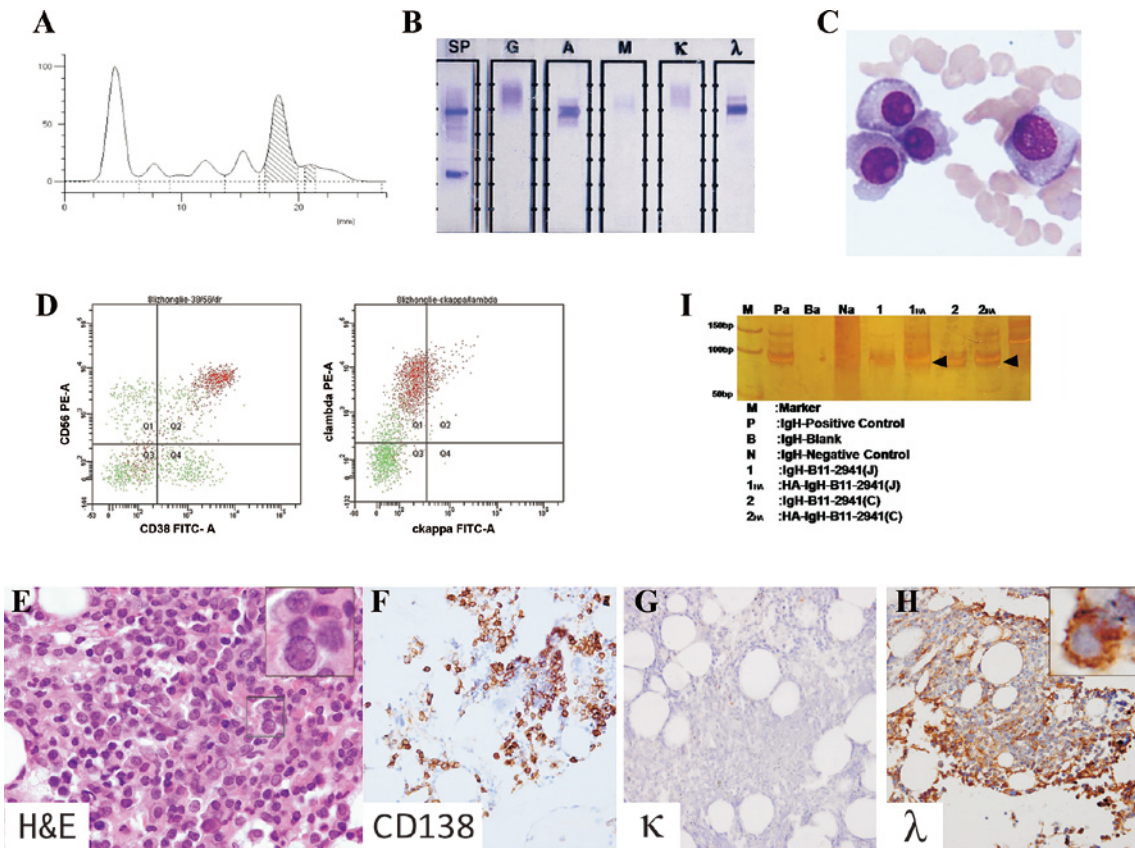


Fig. 2. Plasma cell myeloma.

A. Serum protein electrophoresis reveals a monoclonal protein spike. B. The monoclonal protein was identified as IgA lambda by immunofixation electrophoresis. C. Bone marrow aspirate smears showing the proliferation of immature plasma cells and a rouleaux formation of red blood cells. D. Representative scatter plots from bone marrow flowcytometry, indicating aberrant plasma cells expressing CD38, CD56 and restricted cytoplasmic lambda light chain. E. Hematoxylin and eosin staining of bone marrow trephine biopsy specimen shows a diffuse sheet of malignant plasma cells displacing normal hematopoietic elements (×400; detail in inset). Immunostaining of the bone marrow using anti-CD138 (F), anti-κ (G) and anti-λ (H) antibodies reveals strong CD138 and λ expression in plasma cells (×400; insets ×1,000). I. Clonality study using the BIOMED-2 IgH gene rearrangement assay. A heteroduplex analysis of the bone marrow shows clonal bands in lanes 1A and 2A in duplicate (arrows).

positive plasma cells (Fig. 2E and F), with restricted expression of lambda light chain (Fig. 2G and H); however, no involvement of lymphoma cells was observed. A heteroduplex analysis with the BIOMED-2 primer disclosed a positive clonal IgH gene rearrangement (Fig. 2I) (van Dongen et al. 2003).

The existence of distinct monoclonal myeloma cells in the bone marrow overshadowed the presence of malignant T cells in the lymph nodes and obscured the underlying malignancy. Additionally, our differential diagnosis included a preceding monoclonal gammopathy of undetermined significance (MGUS), asymptomatic myeloma followed by AITL or coexistence of myeloma and AITL. Given the patient's medical history and present clinical, laboratory, radiological, and pathological findings, previous plasma dyscrasia was less likely, and a diagnosis of AITL with coexisting plasma cell myeloma was established.

Within two weeks of supportive care, the patient failed to improve, developing abdominal pain and progressive edema. Given the patient's advanced age, the rapid progression of lymphoma, and the coexistence of myeloma, severe infection and multiple comorbidities, chemotherapy was expected to be effective and well tolerated. Therefore, a modified COP chemotherapy regimen consisting of cyclophosphamide (600 mg/m² on day 1), vincristine (2 mg on day 1), and prednisone (50 mg twice a day from day 1 to 5)

was initiated. Thalidomide, a drug with antiangiogenic and immunomodulatory effects, was also administered at 50 mg daily. This regimen induced rapid regression of the lymphadenopathy and a decrease in the serum globulin levels. The patient then remained in partial remission for approximately 3 months and refused further standard chemotherapy. When his disease later progressed, the patient received a second course of chemotherapy but died of pneumonia 6 months after diagnosis.

Discussion

Here, we describe a patient who presented with typical clinical features of AITL, including generalized lymphadenopathy, hypergammaglobulinemia, and a positive Coombs test. Distinct pathological findings and clonal TCR gene rearrangement in the lymph nodes confirmed the diagnosis of AITL. Additionally, anemia, a high serum monoclonal paraprotein level and clonal plasmacytosis in the bone marrow indicated the coexistence of a plasma cell neoplasm. Myeloma was regarded as the major cause of the anemia, which was supported by malignant plasmacytes infiltration in the bone marrow and the lack of evidence for hemolysis.

In the past decade, various hematologists have noted a relationship between AITL and plasma cell proliferation, as presented in Table 1. Awareness of this relationship is important for differential diagnosis. In total, 8 of 12

Table 1. Case reports of AITL and associated plasma cell proliferations.

Reference	Case No. / Sex/Age(y)	Pattern of plasma cell proliferation	Site of plasma cell proliferation	Interval (mo)	IgH/light chain restriction	EBER	Treatment	Follow-up (mo)
(Yamane et al. 2007)	1/M/63	Polyclonal	PB, BM	N	PC/NA	–*	COP, steroids	AIR (17)
(Sakai et al. 2007)	2/M/73	Polyclonal	PB, BM	N	ND	ND	steroids	DD (< 1)
(Ahsanuddin et al. 2011)	3/F/76	Polyclonal	PB, BM	N	PC/NA	NA	NA	NA
	4/F/43	Polyclonal	PB, BM	72	PC/NA	NA	NA	NA
	5/M/60	Polyclonal	PB, BM	N	PC/NA	NA	NA	NA
(Nagoshi et al. 2013)	6/F/75	Polyclonal	PB, BM	N	NA	NA	CHOP	AIR (23)
	7/M/60	Polyclonal	PB, BM	N	NA	NA	CHOP, CsA+Dex	AIR (10)
	8/M/68	Polyclonal	PB, BM	N	NA	NA	CHOP, CHASE	AIR (102)
(Balague et al. 2007)	9/F/70	Clonal	LN	N	MC/lamda	–	R-CHOP	AWD (39)
	10/M/56	Clonal	LN	N	MC/lamda	–	NA	NA
(Huppmann et al. 2013)	11/F/60	Clonal	LN	N	MC/kappa	–	ECHOP	NA
(Zettl et al. 2002)	12/M/61	Clonal (plasmacytoma)	LN	96	OC/NA [†]	+ [‡]	NA	AWD (24)

*In the LN and BM samples, only a few scattered cells were positive for EBER.

[†]Clonality study of the plasmacytoma displayed monoclonal TCR rearrangement with a length identical to one of the two bands of the biclonal AITL.

[‡]EBER was positive for the transformed large B cells in the AITL and also positive for the plasma cells in the plasmacytoma.

PB, peripheral blood; BM, bone marrow; PC, polyclonal; NA, not available; AIR, alive in remission; ND, not done; DD, die of disease; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CsA, cyclosporine A; Dex, dexamethasone; CHASE, cyclophosphamide, cytosine arabinoside, etoposide and dexamethasone; LN, lymph node; MC, monoclonal; R-CHOP, CHOP combined with rituximab; AWD, alive with disease; ECHOP, CHOP combined with etoposide; OC, oligoclonal.

N: AITL and plasma cell proliferation were simultaneously detected at initial diagnosis.

reported cases of AITL with plasma cell proliferation were accompanied by reactive polyclonal plasmacytosis in the peripheral blood and bone marrow, mimicking plasma cell leukemia. The reactive plasmacytes commonly exhibited a CD19⁺, CD38⁺, CD138^{+/+}, CD10⁻, CD20⁻, and CD56⁻ immunophenotype (Sakai et al. 2007; Yamane et al. 2007; Ahsanuddin et al. 2011; Nagoshi et al. 2013). In addition, 4 of 12 patients demonstrated proliferation of monoclonal plasma cells that were relatively mature in morphology; that originated from EBV-negative clones; and that were always associated with AITL lesions at the lymphoma site, but not in the bone marrow (Zettl et al. 2002; Balague et al. 2007; Huppmann et al. 2013). However, the potential mechanism involved in the development and progression of the concomitant plasma cell proliferation remains to be clarified. High levels of cytokines, such as IL-6, IL-10 and tumor necrosis factor- α , may serve as possible contributing factors (Balague et al. 2007; Sakai et al. 2007; Yamane et al. 2007; Ahsanuddin et al. 2011; Huppmann et al. 2013; Nagoshi et al. 2013).

In addition, according to various, sporadic reports, multiple myeloma is occasionally associated with other peripheral T-cell lymphoma subtypes, including cutaneous anaplastic large T-cell lymphoma, Sezary syndrome, mycosis fungoides, and primary T-cell lymphoma of the bone (Bryant et al. 1982; Weiss et al. 1984; Brumana et al. 1993; Cartron et al. 1999; Wickenhauser et al. 1999; Takami and Mizunoya 2000; Gernone et al. 2002; Hwang et al. 2008; Tangour et al. 2011). In general, the secondary myeloma occurs several years after the initial diagnosis and the subsequent treatment of the T-cell lymphoma (Bryant et al. 1982; Weiss et al. 1984; Brumana et al. 1993; Wickenhauser et al. 1999; Gernone et al. 2002; Zettl et al. 2002; Hwang et al. 2008). Various authors have suggested that the secondary neoplasms are potentially related to immunoregulatory disturbances caused by the primary lymphomas and that the malignant plasma cells may evolve from a sustained inducing stimulus provided by the neoplastic T cells.

To the best of our knowledge, the simultaneous occurrence of de novo AITL and plasma cell myeloma has not been previously reported. Despite the very slight probability that the two distinct neoplasms occurred simultaneously, we assume that this case is a prototype of the interplay between malignant T cells and plasma cell proliferation. The presence of EBV was confirmed in the nodal sample using in situ hybridization for EBV-encoded small RNAs (EBERs) (Fig. 1G), whereas the bone marrow tissue was EBV negative (data not shown). Thus, we hypothesize that the clonal expansion of plasma cells occurred via an EBV-independent mechanism, as Balague et al. (2007) previously reported. Further immunohistochemical studies demonstrated strong expression of IL-6 in both node and bone marrow samples (data not shown), which suggests that the high levels of IL-6 released from AITL lesions could act systemically and play a possible pathogenic role in the bone marrow. In contrast to previously reported cases that

showed clonal plasma cell expansion was topographically related to AITL, the two neoplasms in our patient arose at different anatomical sites. Moreover, the positive B-cell clonality in the bone marrow and the negative B-cell clonality in the lymph node implied that the microenvironment of the bone marrow, as opposed to that of the lymph node, is indispensable for the clonal evolution of plasma cells. In conclusion, we hypothesize that cytokines, disturbed immunoregulation and neoplastic T cells may potentially provide sustained stimulation for polyclonal plasma cell expansion, which is followed by the proliferation of a monoclonal plasma cell population that is probably regulated by an unknown aspect of the bone marrow microenvironment.

It has been noted that polyclonal or clonal plasma cell proliferation that is associated with underlying AITL might be a distinctive phenomenon in this condition, and it is advisable to consider AITL in the differential diagnosis of generalized lymphadenopathy with various manifestations of plasma cell proliferation. Given the rarity of the coexistence of AITL with a plasma cell neoplasm, further studies are necessary to clarify the interplay between the two malignancies, and a detailed evaluation of clonality is essential for differential diagnosis.

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Conflict of Interest

The authors declare no conflict of interest.

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