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*Review Article*

# Tumor-forming plasmacytoid dendritic cells in acute myelocytic leukemia: a report of three cases and literature review

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**Abstract:** Plasmacytoid dendritic cells (PDCs), through their production of type I interferons (IFNs) and other pro-inflammatory cytokines, link the innate and adaptive immunity, and provide anti-viral resistance. It is reported PDCs accumulated in inflammatory and human neoplasms, including hematopoietic malignancies. To date, the clinical significance of tumor-forming PDCs (TF-PDCs) in AML is largely unknown. Here, we designed an integral scheme using flow cytometry, by which we accurately have detected the TF-PDCs in cases of AML. Combined the case characters and progress, we suggested that: TF-PDCs in AML maybe originate from the bone marrow mononuclear precursor cells, so it often associated with mononuclear line-related myeloid tumors; the accumulation of PDCs indicated highly aggressive tumor with poor progress and probably potential myelodysplasia or dysplasia.

**Keywords:** Plasmacytoid dendritic cell (PDC), tumor-forming plasmacytoid dendritic cell (TF-PDC), acute myeloid leukemia (AML), flow cytometry (FCM)

## Introduction

Dendritic cells (DCs) are antigen-presenting cells, named for their dendritic-like morphology in cell morphology [1]. DCs originated from bone marrow pluripotent hematopoietic stem cells, and gave rise to plasmacytoid dendritic cells (PDCs) and myeloid dendritic cells (MDCs). PDCs secrete high amounts of type 1 interferon (IFN), especially IFN-α, playing key roles in innate and adaptive immunity. PDCs accumulate in a variety of inflammatory conditions, including Kikuchi-Fujimoto lymphadenopathy, hyaline-vascular Castleman disease, and autoimmune diseases, and in certain malignancies such as classical Hodgkin lymphoma, chronic myelomonocytic leukemia and carcinomas [2]. PDCs often also infiltrate in the skin, lymph nodes, spleen and bone marrow of patients with myeloid neoplasms, a relatively rare condition now defined as "tumor-forming PDCs" (TF-PDCs for short). In addition, TF-PDCs rarely are reported in AML, and the clinical significance of its changes needs to be further explored. Here we report three case of AML associated with TF-PDCs.

## Case presentation

### *Case 1*

A 67-year-old man was hospitalized with the chief complain being dizziness, and fatigue for 3 years. Physical examination showed no sternal tenderness, lymphadenectasis and no nodules, plaques or abrasions and other skin lesions. Laboratory results included white blood cell (WBC) count $9.60\times10^9$/L, hemoglobin concentration (HB) 45 g/L, platelet concentration (PLT) $33\times10^9$/L. Bone marrow aspiration biopsy showed a large number of primitive granulocytes and primitive immature mononuclear cells (54.5%). displaying cytological features suggestive of acute myelomonocytic leukemia (AMML, M4). In addition, morbid hematopoiesis

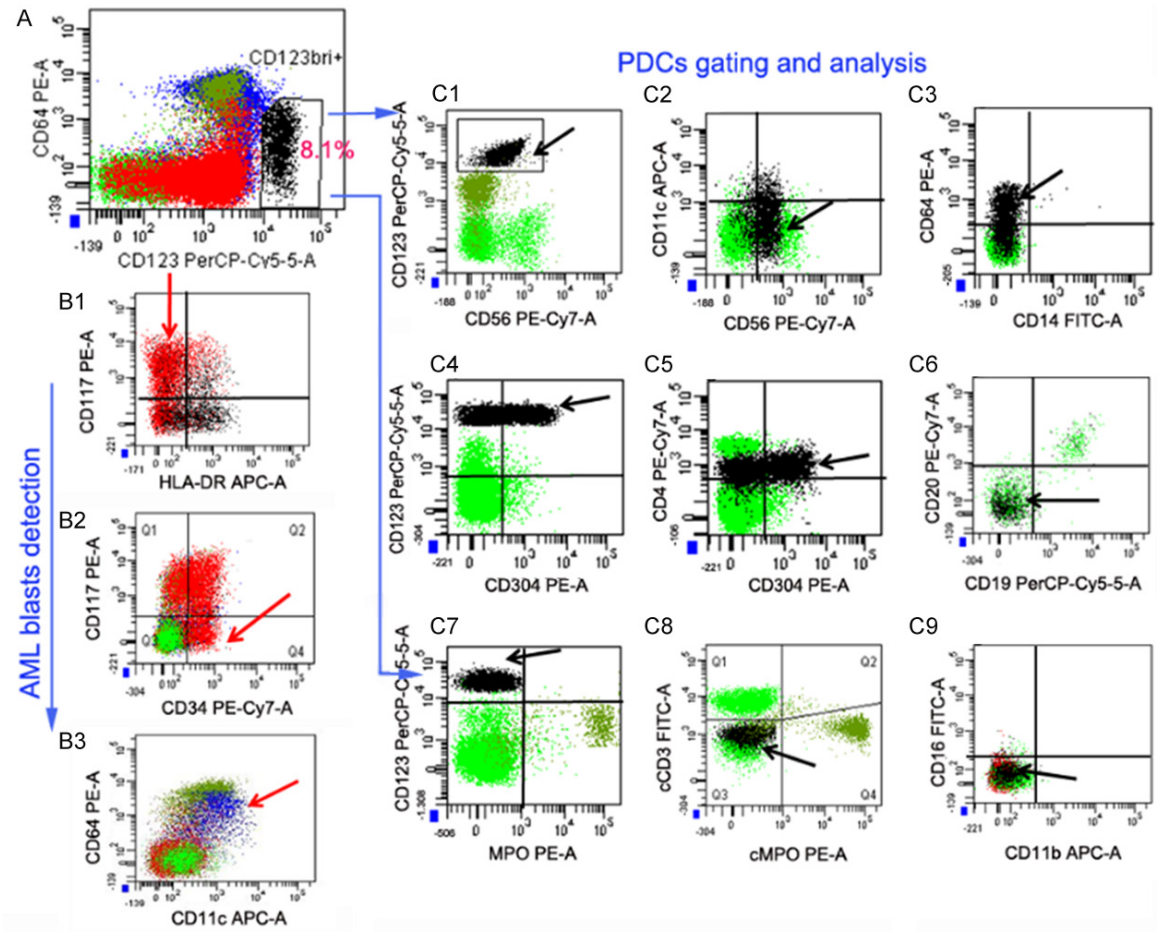


**Figure 1.** Two-step FCM analysis schema in AML. Taking the first patient as an example, (A and B) demonstrated the AML blasts, expressing $CD117^{+}$ $HLA\text{-}DR^{-}$ $CD34^{+}$ $CD123^{+}$, and partial cells display the immunophenotype of granulocytes and monocytes, expressing $CD123^{+}$ $CD64^{+}$ $CD11c^{+}$ (B1-B3). Secondly, $CD123^{bri+}$ cells were found from the primordial myeloid cell population in (A), accounting for 8.1%, then gating on the CD123 positive cells, immunostaining suggested $CD56^{dim}$ $CD11c^{-}$ $CD64^{par+}$ $CD14^{-}$ $CD304^{+}$ $CD4^{dim}$, negative for the marker of T cell, B cells and myeloid cells, such as CD19, CD20, CD14, CD16, MPO, and cCD3 (C1-C9), normal lymphocyte (Green) as the internal control.

can be seen in all stages of granular, erythroid, and megakaryocyte cell. For example, Pseudo-Pechs deformity of ranular cells, Petal--like nuclear deformity of erythroid cells and small megakaryocytes, multinucleated round nucleus megakaryocytes. 5q-positive cells in bone marrow samples accounted for 18% by FISH detection. Chromosome karyotype analysis: 46XY 5q-, -18, +mar.

By flow cytometric, myeloid primordial cells were found, some of whom expressed the monocyte markers CD14, CD64, and CD11c. Noteworthy, $CD123^{+}$ cells accounted for 8.1% in all the nucleated cells. Further staining showsthat $CD4^{+}$ $CD56^{dim}$ $CD123^{bri+}$ $CD11c^{-}$ $CD304^{+}$ $CD64^{dim}$ $CD141^{+}$ $CD34^{-}$ $CD117^{-}$ $CD38^{-}$ (**Figure 1**). Finally this case was diagnosed by acute myelomonocytic leukemia, with myelodysplasia-related change (AMML-MRC), associated with PDCs. The patient gave up treatment and was discharged.

*Case 2*

A 28-year-old man was hospitalized with the chief complain being thin, and fatigue for 3 months. Laboratory results included WBC count $4.47\times10^{9}$/L, HB 46 g/L, PLT $8\times10^{9}$/L. Bone marrow aspiration showed that primitive immature mononuclear cells accounted for 36%, eosinophils increased to 27.5%. CBFβ/MYH11 fusion gene (79%), +8 (79%) and +22 (84%) karyotype were detected by FISH. Chro-

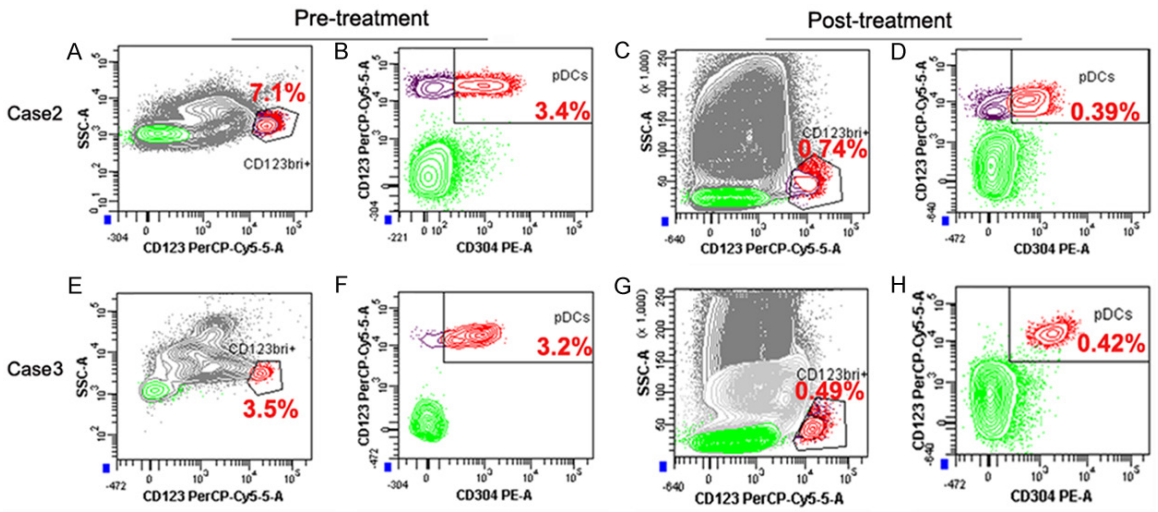


**Figure 2.** The changes in PDCs, before and after the treatment. (A-D) Reflects the second case, and (E-H) displays the third case. (A and B) Represent respectively the proportion of $CD123^+$, and $CD123^+$ $CD304^+$ at the diagnosis, before the treatment. (C and D) Represent the corresponding proportion after treatment. Similarly, (E and F) denote the second patient's PDCs before treatment, then (G and H) mean the change after treatment. From this figure, it can be seen that PDCs expression increased at the diagnosis, then decreased after therapy.

mosome karyotype analysis showed: 48XY, +8, inv(16)(p13q22), +22.

Through flow cytometric detection, $CD34^+$ $CD117^+$ myeloid primordial cells increased, some of them expressed the monocyte markers CD14, CD64, and CD11c. Like the case 1, $CD123^+$ cells also be found, accounting for 7.1%. Further staining shows that $CD4^+$ $CD56^{dim}$ $CD123^{bri+}$ $CD11c^-$ $CD304^+$ HLA-$DR^+$ $CD34^-$ $CD117^-$ $CD38^-$. This case was diagnosed by AML (M4EO), associated with PDCs. The patient has been given IA (Idarubicin and cytarabine) scheme for chemotherapy, then got complete remission, followed by allogeneic stem cells transplantation in September of 2016, till now, Minimal residual disease (MRD) was sustained negative. The proportion of PDCs, expressing both CD123 and CD304, decreased to 0.39% from 3.4% at Initial diagnosis (**Figure 2**).

*Case 3*

A 59-year-old man was found white blood cell increased for one month and hospitalized. A dark brown skin nodule can be seen at right ankle joint. Laboratory results included WBC count $32.50\times10^9$/L, HB 71 g/L, PLT $9\times10^9$/L. A large number of primitive immature mononuclear cells were found in peripheral blood. Bone marrow aspiration showed that primitive immature mononuclear cells accounted for 23.5%, eosinophils increased to 6.1%. CBFβ/MYH11 fusion transcripts were detected by FISH and RT-PCR. Chromosome karyotype analysis: 46XY, inv(16)(p13q22).

By means of flow cytometric analysis, some of $CD34^+$ $CD117^+$ myeloid primordial cells also expressed the monocyte markers CD14, CD64, and CD11c. $CD123^+$ cells also be found, accounting for 5.1%. Further staining showed that $CD4^+$ $CD56^{dim}$ $CD123^{bri+}$ $CD11c^-$ $CD304^+$ HLA-$DR^+$ $CD34^-$ $CD117^-$ $CD38^-$. This case was diagnosed by AML (M4EO), associated with PDCs. The patient has been given two IAE (Idarubicin, cytarabine and etoposide) schemes for chemotherapy, then got partial remission, whereas the MRD was sustained positive. The proportion of PDCs, expressing both CD123 and CD304, decreased to 0.42% from 3.2% at Initial diagnosis (**Figure 2**).

## Discussion

Dendritic cells are bone marrow-derived leukocytes that are responsible for the initiation of immune responses and exert a sentinel-like function [1]. PDCs are a subset of the heterogeneous dendritic cell family that serve a critical role in the immune system as pathogen sensors and activators of adaptive immunity. PDCs account for approximately 0.01% to 0.05% of

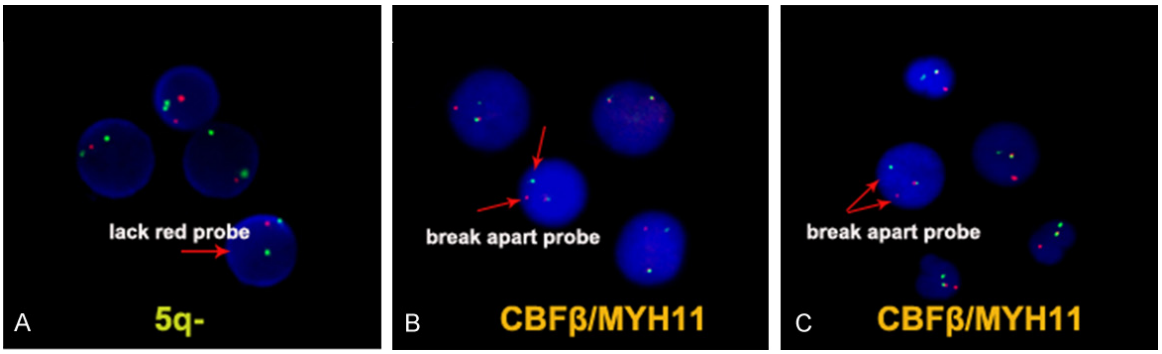


**Figure 3.** The Chromosomal abnormality in PDCs. The PDCs from each case was sorted out firstly, and then detected by FISH. A: Denotes that 5q-positive cells were found in the PDCs of first case. B and C: Show that CBFβ/MYH11 fusion transcripts still exist in the PDCs of the second and third patients.

peripheral blood mononuclear cells and accumulate in inflammatory sites to contribute to the ongoing inflammatory response [2].

Rarely, PDCs may also accumulate in the skin, lymph nodes, spleen and bone marrow of patients with myeloid leukemia, a yet poorly known condition currently called "tumor-forming PDC associated with myeloid neoplasms" [3]. In this study, we found PDCs increase in the three AML bone marrow samples. Then we specially sorted out the subset of PDCs and discovered also the same chromosomal abnormalities with the other leukemia blasts by FISH, respectively 5q-positive in PDCs of first patient and CBFβ/MYH11 fusion transcripts in PDCs of the second and third patient (**Figure 3**). So it is suggested this subset as "tumor-forming PDC" in our report. Meanwhile, we detected the PDCs in bone marrow samples from 16 healthy transplantation donors as control, as a result, the mean PDCs accounted for 0.08% (0.03%-0.27%) (data not shown). Anyway the function of increased PDCs in AML needs to explore. Based on the literatures, PDCs, through their secretion of type I IFNs and other cytokines, are implicated in a wide variety of immune functions, including antiviral immunity, antitumor immunity, and peripheral tolerance [4]. But tumor microenvironment can subvert this property. PDCs in the tumor bed are apparently disarmed in their capability to produce the required amount of I-IFN. This inhibition is likely dependent on the abundance of ligands to inhibitory receptors on cancer cells or on cells of the tumor microenvironment [5].

TF-PDCs should be differentiated from blastic plasmacytoid dendritic cell neoplasm (BPDCN). BPDCN is a rare hematologic malignancy which was first included as an independent cutaneous lymphoma in the 2008 World Health Organization (WHO) classification [6]. The clinical hallmarks of BPDCN are predominant cutaneous involvement, with subsequent or simultaneous extension to bone marrow and peripheral blood. About 15-20% of BPDCN cases develops into a myelomonocytic leukemia or acute myeloid leukemia [7, 8]. TF-PDCs and BPDCN possess similar Immunophenotype and biological behavior. It has been shown that immunophenotypic profiles of normal PDCs mainly expressed $CD123^{+}$ $CD4^{+}$ $TCL1^{+}$ $CD56^{-}$ $TdT^{-}$ Ki67<5%, TF-PDCs expressed $CD123^{+}$ $CD4^{+}$ $TCL1^{+}$ $CD56^{+/-}$ $TdT^{-}$ Ki67<10%, and BPDCN expressed $CD123^{bri+}$ $CD4^{+}$ $TCL1^{+}$ $CD56^{+}$ $TdT^{+/-}$ Ki67>30% [2].

How to identify the TF-PDCs from the AML sample accurately by flow cytometry? We firstly design a scheme including markers CD14/CD64/CD123/CD56/CD11c/CD45 to detect the monocytes, next add the immune markers CD123, CD303 or/and CD304 to gain the PDCs that expressed $CD4^{+}$ $CD56^{dim}$ $CD123^{bri+}$ $CD11c^{-}$ $CD304^{+}$ $CD34^{-}$ $CD117^{-}$ $CD38^{-}$ (**Figure 1**). Three cases of AML associated with pDCs were found in 268 AML samples from Nov 2013 to Sep 2016 in our laboratory, accounting for 1.13%. Combined the clinical symptoms and immune phenotype, we diagnosed these AML associated with PDCs, not the BPDCN or PDCL [9]. The ratio of PDCs is different with diverse hematological neoplasms. Laane, E. et al, [10] reported that children with T-ALL had significantly higher numbers of PDCs than children with preB-ALL. Mohty, M. et al, [1] found that PDCs increased in 4 case of AML, consistent with our report (**Table 1**), but the significance of this is

**Table 1.** TF-PDCs in AML

| Author | Patient (y/s) | Diagnosis | Clinical presentation | PDCs (%) | Immune phonotype | Treatment | Prognosis |
|---|---|---|---|---|---|---|---|
| Mohty, M [1] | NA | AML (1 M1, 1 M3, 2 M5) | NA | 7.28 | FC $lin^-/CD11c^-/ILT3^+$. | NA | NA |
| Dargent J.L [11] | 72/m | AML | Multiple papules or erythematous plaques scattered on the skin. | NA | Skin biopsy IHC: Positive: CD4, CD43, CD68, CD123, granzyme B, CD303, TCL1, CD2AP. Negative: CD3, CD10, CD20, CD34, CD56, CD117, CD138, CD163, myeloperoxidase, 3 tryptase, WT1, TdT. | Supportive therapy daily; 6-mercaptopurine, and mito-xantrone when necessary. | Alive 8 months after the diagnosis |
| Song H.L [12] | 55/m | AML-M0 | Enlarged lymph nodes over the retroauricular, cervical, axillary and inguinal regions. | NA | IHC: positive CD43, CD68 CD4, and CD123. | Chemotherapy with cytarabine and idarubicin (I3A7 regimen). | Died 17 days after admission. |
| Vermi M [13] | 50/M<br>86/M<br>62/F | AML-M4<br>AML-M5<br>AML-M5 | Leukocytosis, anemia lymphocytosis, thrombocytopenia, anemia Pancytopenia. | NA | IHC: positive HLA-DR, CD4, CD45RA, CD68, CD68R, CLA/HECA/452, and CD123. | NA | 11 Months alive 3 Months alive 15 months |
| Ping.W (this paper) | 67/M | AML-MRc | Anemia | 8.1 | FC: $CD123^{bri}$ $CD4^{dim}$ $CD56^{dim}$ $CD304^+$ $DR^+$ $CD141^+$ $CD36^+$ $CD9^-$ $CD34^-$ $CD117^-$ MPO-$cCD3^-$ $CD79a^-$ $CD11c^-$ $CD19^-$ $CD10^-$ $CD22^-$ $CD1c^-$. | Without treatment | NA |
| Ping.W (this paper) | 28/M | AML-M4Eo | Anemia | 7.1 | $CD123^{bri}$ $CD4^{dim}$ $CD56^{dim}$ $CD304^+$ $DR^+$ $CD34^-$ $CD117^-$ $CD9^-$ $CD64^-$ $CD38^-$ $MPO^-$ $cCD3^-$ $CD79a^-$ $CD11c^-$ $CD19^-$ $CD10^-$ $CD22^-$. | IA (2 cycles), followed by ASCT | Alive |
| Ping.W (this paper) | 59/M | AML-M4Eo | Leucocytosis, anemia | 6.1 | $CD123^{bri}$ $CD4^{dim}$ $CD56^+$ $DR^+$ $CD64^{dim}$ $CD34^-$ $CD117^-$ $CD11c^-$ $CD38^+$ $MPO^-$ $cCD3^-$ $CD79a^-$ $CD19^-$ $CD10^-$ $CD22^-$. | IAE (2 cycles) | Alive |

unknown. In our experiment, the TF-PDCs chromosome abnormality are same with leukemic blasts, meanwhile, the TF-PDCs population express the $CD56^{dim}$ positive. The CD56 expression is negative in normal PDCs, CD56 positive suggested cancerization. Combined other reports [11-13], it demonstrated that PDCs increase in AML maybe denote poor prognosis (**Table 1**). Nodules of PDCs occur in up to 20% in the bone marrow biopsies of CMML, which demonstrated to be clonally related to myelomonocytic lineages [14]. Interestingly, the subtype of AML we reported is also correlative to monocytic lineage. It is speculated that AML associated with PDCs increase might prone to monocytic lineage pathologic changes.

The first patient in our paper was diagnosed AMML-MRC, whose bone marrow sample displays obvious morbid hematopoiesis and 5q- chromosome abnormality. It maybe the MDS transformed AML. Mongkonsritragoon, W et al [15] and Ma L, et al [16] found the PDCs in MDS bone marrow samples and detected abnormal karyotype in PDCs, same with the other myeloid subset karyotype. Therefore we think that DCs, originated from MDS cell clones, produced myeloid lineage hematopoietic disorder, induced blood cell reduction. The abnormality of DCs maybe one reason of Immunodeficiency in MDS patients. Whether or not the AML associated with PDCs is accompany with myelodysplastic dysplasia, needs to further validation. The physical examination of the third patient revealed skin nodule in ankle joint. The PDCs expressed $CD56^{dim}$ $CD38^{+}$ by flow cytometry. CD38 in CLL [17], MM and other hematological neoplasms [18] is a marker of poor prognosis. Vermi, W et al [13] demonstrated that nodal and extranodal PDCs share the same chromosomal abnormality, indicating that TF-PDCs are clonal, neoplastic in nature, and closely related to the associated myeloid tumor. Hence, it is supposed that AML associated PDCs is easy to transfer to distant lymph nodes, skin, spleen, and other organs. Since TF-PDCs accumulation in myeloid tumor indicates poor prognosis, Bendamustine [19], 5-Azacytidine [6] and ASCT [20] were tried to treat this kind of myeloid tumor and got optimistic outcome.

## Conclusion

We reported 3 cases of TF-PDCs in AML. Combined our experimental data and literature review, it is believed that TF-PDCs accumulated with AML maybe sign of poor prognosis. Secondly, AML associated with increased PDCs are might prone to monocytic lineage pathologic changes. Lastly, TF-PDCs are clonal, neoplastic in nature, and closely related to the associated myeloid tumor, which are easy to transfer to distant lymph nodes, skin and other organs.

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## Disclosure of conflict of interest

None.

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