

Case Report

Primary pulmonary NK/T cell lymphoma: report of a rare entity and review of literature

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Abstract: Primary pulmonary NK/T cell lymphoma is extremely rare. The authors reported a case of primary pulmonary NK/T cell lymphoma in a 47-year-old man presented with fever, cough, and chest pain. Morphologically, an angiocentric/angiodestructive growth pattern with coagulative necrosis was observed. On immunohistochemical staining, the atypical lymphocytes showed TIA-1+, CD56+, Ki-67 40%+, Cytokeratin-, CD30-, ALK- and CD20-. In Situ hybridization, most atypical lymphocytes had positive staining for Epstein-Barr virus encoded RNA. All of above findings were consistent with NK/T cell lymphoma. The patient's general status was improved after chemotherapy of VIPD. We also reviewed the clinical and pathological characteristics of primary pulmonary NK/T cell lymphoma which have been published in the literature.

Keywords: NK/T cell lymphoma, primary pulmonary lymphoma, lymphoma, Epstein-Barr virus

Introduction

Primary pulmonary lymphoma (PPL) is a rare disorder representing only 0.5-1% of all primary pulmonary malignancies, less than 1% of all cases of *non-Hodgkin's* lymphoma (NHL), and 3-4% of extranodal NHL. The majority of PPL are B-cell lymphoma arisen from bronchial mucosa associated lymphoid tissue [1]. Primary pulmonary NK/T cell lymphoma may share similar symptoms and radiographic observations with pneumonia or carcinoma [2, 3]. Histopathologically, its lesions usually show extensive coagulative necrosis and infiltration of lymphocytes with a broad cytologic spectrum and may be easily misdiagnosed as chronic inflammation if immunohistochemistry (IHC) staining is not performed or large numbers of specimens are not carefully evaluated by pathologists. As far as we are aware, there are only 10 cases which have been reported in the *published literature*. We herein present the case of primary pulmonary NK/T cell lymphoma in a 47-year-old man, and the previous cases are also reviewed.

Case presentation

A 47-year-old Chinese male who presented with a 2-month history of fever, cough, and chest

pain was admitted to a local hospital because of showing no response to oral antibiotic therapy. A chest computed tomography (CT) scan revealed a soft tissue mass (4.5 × 3.1 cm) in the lingual segment of left upper lobe and multiple nodules in both lower lung lobes. No mediastinal or hilaradenopathy was noted (**Figure 1A-C**). A sputum smear showed gram-positive streptococcus pneumoniae. Percutaneous transthoracic needle biopsy of the mass showed extensive coagulative necrosis and scattered small lymphocytes, by means of which and without IHC staining, the patient was initially diagnosed as chronic inflammation. The patient was treated with antibacterial (mezlocillin/sulbactam, levofloxacin and linezolid for 14 days), antifungal and antitubercular drugs successively, none of which worked.

The patient was then transferred to other hospital. A positron emission tomography computed tomography (PET/CT) scan confirmed multiple intense hypermetabolic uptakes in both lung fields, without other identifiable adenopathy. A surgical resection of the mass and nodules was performed. The pathology also revealed extensive coagulative necrosis with multifocal mixed inflammatory cells infiltration (**Figure**

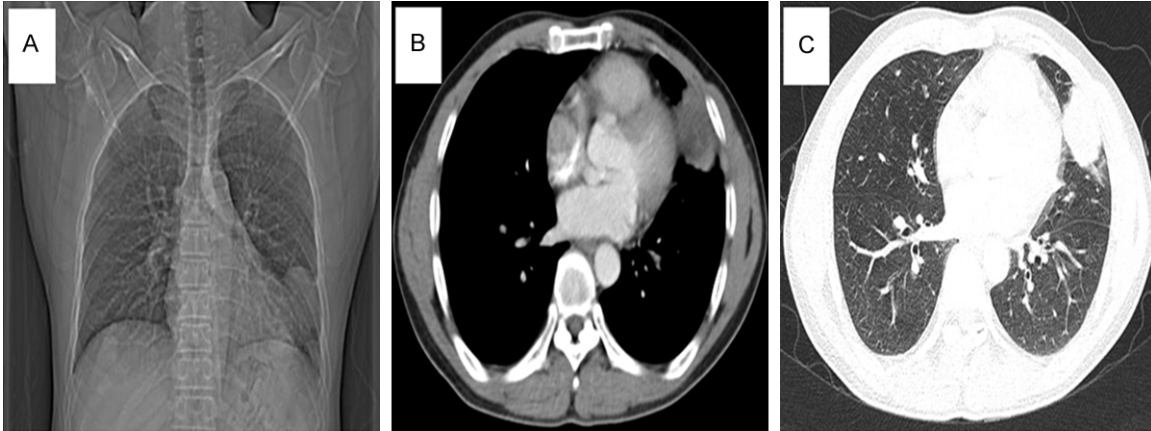


Figure 1. A chest X-ray and CT taken in a local hospital. A: Chest X-ray, B: Enhanced thoracic axial CT scan (mediastinal window), and C: Thoracic axial CT scan (lung window) show multiple bilateral pulmonary nodules with a soft tissue mass, but no mediastinal or hilaradenopathy.

2A). Specific IgM/IgG antibodies to *Sparagnum* were detected. It was diagnosed as parasite infection again following with the treatment of praziquantel.

On admission to our hospital with worsening fever 20 days later, a repeat chest CT scan indicated a recurrent space-occupying lesion (3.6 × 2.8 cm) in the right hilar/perihilar upper lung with mediastinal and hilar lymphadenopathy. Laboratory results were as follows: White blood cell count, 4400/mm³; Platelet count, 112000/mm³; Hemoglobin, 12.5 g/DL; And LDH, 482 U/L. Other laboratory screening (include human immunodeficiency virus (HIV) test, G test, GM test, anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-ENA antibodies, anti-dsDNA antibodies, blood cultures, anti-tuberculosis antibody, bone marrow smear) were all in normal range. Transbronchial biopsy showed extensive necrosis and apoptotic bodies. Special stains were negative for mycobacteria and fungi.

The patient consulted with our pathologists. Previous sections showed small to medium-sized with irregular nuclei and hyperchromatic nuclei lymphocytes infiltrate to vascular walls (**Figure 2B, 2D**). Immunohistochemical results, which were performed for the first time by our department, revealed that CD2, CD3, CD7, TIA-1 and CD56 were positive, whereas CD20, cytokeratin and ALK was negative in the atypical cells. Labeling index of Ki-67 was 40% in the atypical lymphocytes. In situ hybridization

for Epstein-Barr virus encoded RNA (EBER) showed a positive reaction (**Figure 3A-F**), which was consistent with the plasma Epstein-Barr virus (EBV) DNA level (4.32 × 10⁴ copies/ml). After serial studies including nasopharyngoscopy and abdominal CT, it was no evidence of lymphoma found in extrapulmonary site. Primary pulmonary NK/T cell lymphoma was finally diagnosed. Then the patient received three cycles of etoposide, ifosfamide, cisplatin and dexamethasone (VIPD). During 4-month follow-up, the patient's temperature went back to normal and all other symptoms were improved.

Discussion

Extranodal natural killer/T-cell lymphoma (ENKL) is rare. The nasal cavity and paranasal tissue including the upper aerodigestive tract are the most commonly affected area. Lung involvement, usually regarded as the end stage of ENKL [4, 5], as for main manifestation is especially rare [6]. Primary pulmonary NK/T cell lymphoma shares the same pathological characteristics with ENKL. Histologically, atypical lymphocytes are diffused and permeated. It is always found an angiocentric and angiodestructive growth pattern with coagulative necrosis. Atypical lymphocytes, which are diverse in size, from small to large, are mixed with other inflammatory cells [7]. Tumor cells stained positively for CD3, CD56, TIA-1. The etiology of ENKL has shown strong association with EBV, thus, EBER is the most reliable standard in diagnosis of ENKL [7]. However, extensive necrosis, mixed-cell, and without performance

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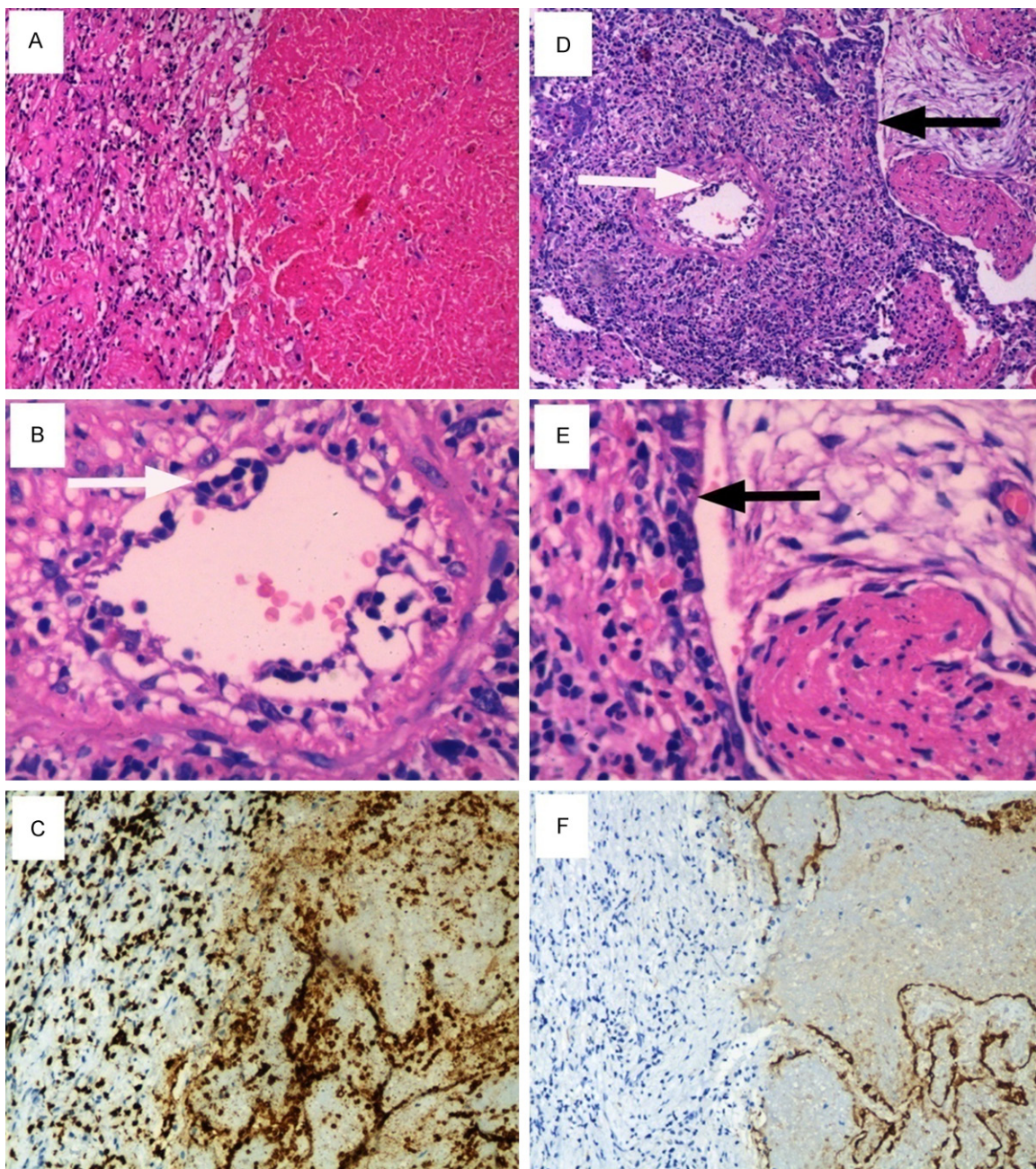


Figure 2. The white arrows point to regions, where the atypical cells infiltrate into the vascular wall. The black arrows indicate pseudo-epitheliomatous hyperplasia. A. Extensive coagulative necrosis with lymphocytes infiltration ($\times 100$). B. Small to medium size lymphocytes with irregular nuclei and hyperchromatic nuclei ($\times 400$). C. IHC staining of CD3 showed infiltration of CD3+ lymphocytes in the same area as A ($\times 100$). D. Angiocentric growth pattern and pseudo-epitheliomatous hyperplasia ($\times 100$). E. High-magnification view of pseudo-epitheliomatous hyperplasia ($\times 400$). F. CK staining revealed the presence of necrotic pulmonary alveolar in the same area as A ($\times 100$).

of IHC staining are the most common causes of delay in the diagnosis of ENKL.

In the present case, we observed special morphological features, which may be the clues for diagnosis of primary pulmonary NK/T cell lymphoma.

In necrosis area, H&E staining and expression of CD3 and CK revealed neoplastic lymphocytes infiltrating and pulmonary alveolar necrosis (Figure 2A, 2C and 2F). Necrosis is not the reason to give up performing IHC stains, and on the contrary, it may reflect on the nature

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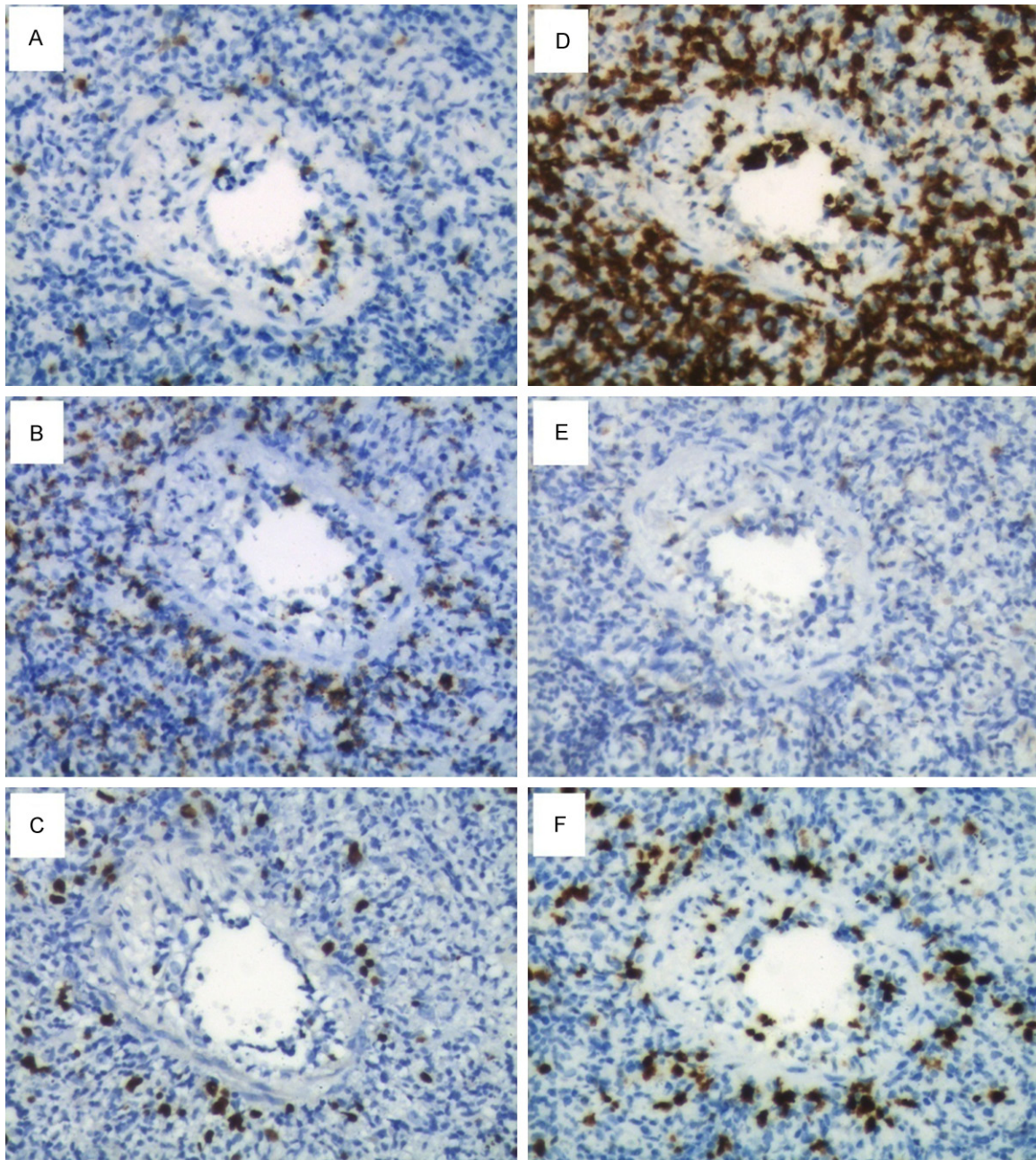


Figure 3. IHC staining observation. A. CD20 staining presented negative reaction in atypical cells ($\times 200$). B. IHC stains showed positive reactivity for TIA-1 ($\times 200$). C. In situ hybridization for EBER showed positive reaction in atypical cells ($\times 200$). D. IHC stains showed positive CD3 ($\times 200$). E. The expression status of CD56 ($\times 200$). F. The expression levels of Ki-67 ($\times 200$).

of the lesion. Furthermore, pseudo-epitheliomatous hyperplasia is an uncommon morphological feature of ENKL [7]. Atypical hyperplasia of alveolar epithelium was also found in our case (Figure 2D, 2E).

Primary pulmonary NK/T cell lymphoma is uncommon. A review of the literature found

only a few reported cases in China, Taiwan, Japan, Korea, and the United States (Table 1). The geographic distribution is similar to ENKL [7]. Most patients are initially presented with fever and cough, which leads to misdiagnosis as pneumonia. Including the current case, an elevated LDH was found in 9 patients, and positive results of EBV via plasma test or in situ

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Table 1. Nationality, clinical features, diagnostic procedure, treatment and outcome in 11 patients

Reference	Nationality	Clinical features	Diagnostic procedure	Treatment and outcome
Laohaburanakit [8]	American	Fever, cough, and shortness of breath	Transbronchial biopsy (negative)→Transthoracic needle biopsy (suspicious)→Postmortem examination (positive)	Died
Byung Hoon Lee [9]	Korean	Fever, cough, and dyspnea LDH↑, EBV (+), BR (normal)	Transthoracic needle biopsy	Died
Xiao [10]	Chinese	Fever, cough, and dyspnea LDH↑, EBV (+), BR↓	Transthoracic needle biopsy	Died
	Chinese	Fever, cough, and dyspnea LDH↑, EBV (+), BR↓	Transbronchial biopsy and transthoracic needle biopsy (negative)→IHC staining of the specimen (positive)	Died
Oshima [11]	Japanese	Fever and general fatigue LDH↑, EBV (+), BR (normal)	CT-guided needle biopsy (suspicious)→Postmortem examination (positive)	Methyl prednisolone and cyclophosphamide, died
Gui [12]	Chinese	Fever, cough, and shortness of breath LDH↑, EBV (+), BR (normal)	Transbronchial biopsy	CHOP-L × 5 cycles, complete remission
Liu [2]	Taiwanese	Cough and blood-streaked sputum LDH↑, EBV (+), BR (normal)	Transthoracic needle biopsy	Cyclophosphamide and prednisolone, died
Gong [13]	Chinese	Fever LDH (normal), EBV (+), BR (normal)	Excision biopsy of pulmonary lobe	Died
Sangho Lee [3]	Korean	Fever, cough, and sputum LDH↑, EBV (+), BR (normal)	Transbronchial biopsy	Died
Chien [14]	Taiwanese	Fever, cough, and dyspnea LDH↑, EBV (+), BR (normal)	Transbronchial biopsy	CHOP and ESHAP, died
Present case	Chinese	Fever, cough, and chest pain LDH↑, EBV (+), BR (normal)	Transthoracic needle biopsy (suspicious)→Excision biopsy of lesion (misdiagnosed)→IHC staining of the specimen (positive)	VIPD × 3 cycles, partial remission

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hybridization was in 10. The blood routine (BR) test was normal in 9 patients. 3 in total 11 was diagnosed as the primary pulmonary NK/T cell lymphoma through transbronchial biopsy, 4 through transthoracic needle biopsy, 2 through excision biopsy of pulmonary lobe, and 2 through postmortem examination, 4 of which had been delayed diagnosis or misdiagnosed. Pathologists should carefully investigate the whole lesion when observing extensive coagulative necrosis with atypical lymphocyte infiltration. IHC stains are indispensable for the diagnosis even if the vast majority of specimens show necrosis. Clonal analysis technique based on X-chromosome inactivation mosaicism and polymorphisms at the PGK and AR loci in female somatic cells is helpful for difficult cases [13]. TCR gene rearrangement by PCR-based techniques may not be useful for making diagnosis of NK/T cell lymphoma [13, 15].

The vital antidiastole of pulmonary NK/T cell lymphoma is lymphomatoid granulomatosis (LYG), the latter of which is a rare EBV-driven B-lymphoproliferative disorder [16]. The incidence of LYG is relatively much higher compared to pulmonary NK/T cell lymphoma. LYG is also characterized by an angiocentric and angiodestructive infiltrating process, and comprised of a mixture of small to large lymphocytes with variable cytologic atypia, lacking true granulomatous architecture [16]. Despite the high morphological similarities of pulmonary NK/T cell lymphoma and LYG, immunohistochemically, atypical lymphocytes in LYG express CD20. In our case, the tumor cells were positive for CD3, whereas CD20 was negative (**Figure 3A, 3D**). Based on this point, LYG was not considered.

The prognosis of pulmonary NK/T cell lymphoma is generally poor, and the standard treatment for it has not been determined. P-glycoprotein (P-gp) was found to be overexpressed in ENKL [17]. As both doxorubicin and vincristine, two main components in CHOP, are the substrates of P-gp, ENKL is less likely responsive to CHOP regimen [17]. In the present case, patient was treated with another nonanthracycline-based regimen and achieved partial remission. In addition, some asparaginase-containing regimens have been reported to be effective for this disease [12]. It is known that L-asparagin-

ase hydrolyzes serum asparagines and deprives some cells of the required amino acid to yield anticancer effects in lymphoma cells which lack L-asparagine synthetase.

In summary, the clues that led to the clinical suspicion of primary pulmonary NK/T cell lymphoma included space-occupying lesions, Asians, long-lasting fever, no response to antimicrobial chemotherapy, and elevated plasma EBV DNA and LDH levels. For these patients, adequate specimens and IHC stains are helpful for making a definite diagnosis.

Disclosure of conflict of interest

None.

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