Clinical Profile of 327 patients with Sarcoidosis in India: An Ambispective Cohort Study in a Tuberculosis (TB) Endemic Population

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ABSTRACT

Introduction: Sarcoidosis is a multisystem granulomatous disease with a varied clinical presentation. We describe the clinical characteristics of patients with sarcoidosis from a tuberculosis (TB) endemic setting. Methods: We performed an analysis of the sarcoidosis database at a tertiary care facility in North India. Results: Of the 327 patients, 50.8% were male, with a mean age of 42.8 years (range: 16–70 years). Females were significantly older. 42.6% had comorbidities, of which diabetes (17.1%) was most common. More than half (57.1%) were obese. Serum angiotensin-converting enzyme levels were elevated in 186 (57.9%). Eleven (3.8%) had hypercalcemia, while hypercalciuria was present in 54 (31.7%). The majority (89.9%) were tuberculin skin test negative (<10 mm induration), while 71.9% were tuberculin anergic. 47.7% had normal spirometry, while a restrictive impairment was the most common abnormality (44.6%). Obstruction on spirometry was present in 8.3%. Nearly half (160, 49%) had involvement of an extrapulmonary site. Most patients were (96%) symptomatic. Cough, shortness of breath, fatigue, weight loss, and fever were the predominant symptoms. A majority had Stage 1 (47.7%) sarcoidosis. Two hundred and eighty-seven (87.8%) patients underwent bronchoscopy or endosonographic (endobronchial ultrasound-guided transbronchial needle aspiration [EBUS-TBNA] or transesophageal bronchoscopic ultrasound-guided fine-needle aspiration [EUS-B-FNA]) sampling. A histopathological diagnosis with the demonstration of granulomas was achieved in 90.8%. The diagnostic yield of EBUS-TBNA/EUS-B-FNA was 77.4%. In 13.5% of patients, necrotizing granulomas were present in tissue samples. Conclusion: The clinical profile of patients with sarcoidosis in TB endemic settings has certain differences from nonendemic populations. Bronchoscopy and endosonography allow a confident diagnosis in the majority of patients.

KEY WORDS: Bronchoscopy, endobronchial ultrasound-guided transbronchial needle aspiration, granuloma, inflammation, sarcoidosis, tuberculosis

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INTRODUCTION

Sarcoidosis is a multisystem chronic granulomatous disease of unknown etiology. The condition can affect virtually any organ and has an unpredictable clinical course ranging from spontaneous remission, relapse, and persistent disease activity. A confident diagnosis is established with compatible clinicoradiological findings and the demonstration of noncaseating granulomas in tissue biopsy. The diagnosis can also be made on clinicoradiological grounds when the clinical and imaging features strongly support the diagnosis, along with a response to treatment on follow-up. Thoracic (lungs and intrathoracic lymph nodes) involvement is the most common. Depending on the predominant site of involvement, patients may present to various specialties for initial evaluation. Differentiation of sarcoidosis from tuberculosis (TB) is also challenging, especially in endemic TB settings.

There is variability in disease prevalence and clinical features in different demographic settings. Initially, sarcoidosis was thought to be rare in settings with a high prevalence of TB. Studies have described the clinical profile of patients with sarcoidosis from TB endemic settings like India. Of late, bronchoscopy and endosonographic modalities have emerged as the preferred modalities for the diagnosis of sarcoidosis. Endosonographic modalities include endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), transesophageal bronchoscopic ultrasound-guided fine-needle aspiration (EUS-B-FNA), and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA).

Studies on the clinical profile of large patient cohorts of histologically diagnosed sarcoidosis in TB endemic settings are lacking. We herein describe the clinical profile of 327 patients with a diagnosis of sarcoidosis from a tertiary care and referral facility in New Delhi, India.

METHODS

Study design

The study was an ambispective observational study conducted between March 2018 and July 2019 in a tertiary care referral center’s pulmonary outpatient clinic. The retrospective duration was from January 2013 to February 2018, and the prospective duration was from March 2018 to July 2019. The study protocol (Ref No. IECPCG-127/21.03.2018) was approved by the institutional review board (institute ethics committee). We obtained written, informed consent from all the participants. We excluded patients who declined to participate in the study.

Patients

Patients with suspected sarcoidosis underwent a detailed evaluation, including clinical history, physical examination, blood investigations, spirometry, serum angiotensin-converting enzyme (ACE) levels, and tuberculin skin test (TST). We routinely obtained a chest radiograph and a contrast-enhanced computed tomography (CT) scan of the thorax with high-resolution CT, unless contraindicated. The clinician evaluated for extrapulmonary involvement based on clinical symptoms. A conventional bronchoscopy or endosonography-based approach was the preferred modality for histopathological diagnosis. Conventional bronchoscopy modalities included Endobronchial biopsy (EBB), transbronchial lung biopsy (TBLB), and conventional TBNA. Endosonographic modalities were EBUS-TBNA, EUS-B-FNA, or EUS-FNA-centered approaches. We performed endosonographic aspiration or TBNA if enlarged mediastinal nodes were present on the CT scan. We also performed TBLB and EBB in most patients undergoing endosonographic node aspiration as this approach improves the diagnostic yield. If there was lung parenchymal involvement on CT scan without lymphadenopathy, we performed a TBLB and EBB. The clinician chose other sites for histopathological sampling, based on clinical involvement. Diagnosis of sarcoidosis was established with a compatible clinicoradiological profile, negative microbiological investigations for TB, demonstration of granulomas in tissue biopsy, and a response to treatment at 6 months. In patients without a definitive histopathological diagnosis (absence of granulomas on tissue biopsy) but compatible clinicoradiological profile, the patient was labeled as probable sarcoidosis and treatment initiated. In this group, a final diagnosis of sarcoidosis was made after a careful follow-up and response to treatment at 6 months.

Data management

Data were entered as per the designed pro forma. Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at All India Institute of Medical Sciences, New Delhi. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to standard statistical packages, and (4) procedures for data integration and interoperability with external sources.

Statistical analysis

Data management and analysis software Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.) was used for the analysis. Baseline data were expressed as mean and standard deviation or numbers and percentages. Categorical variables were compared between the groups by Chi-square/Fisher’s exact test. A continuous variable following normal distribution was compared by the t-test, and those not following normal distribution were compared by Wilcoxon rank-sum test.
RESULTS

Baseline demographic, clinical, lung function, and laboratory parameters

Of the 327 patients with a final diagnosis of sarcoidosis, 166 (50.8%) were male. The baseline demographic characteristics are summarized in Table 1. The majority (89.6%) were never smokers. The mean age was 42.8 years (range: 16–70 years), with statistically significantly older age in females (males: 40.6 ± 10.6 years, females: 45.0 ± 10.5 years, P < 0.001). One hundred and thirty-nine (42.6%) patients had associated comorbidity/comorbidities. Diabetes (17.1%) was most common, followed by hypertension (14.9%) and hypothyroidism (12.2%). 57.1% of patients were obese (body mass index [BMI] >25 kg/m²). Nearly a third (30.7%) had a history of having received anti-TB treatment.

Serum levels of ACE were elevated in 186 (57.9%) patients. Eleven (3.8%) patients had hypercalcemia. Elevated levels of liver transaminases (serum alanine transaminase) were observed in 114 (34.9%) patients, while 111 (33.9%) had elevated serum alkaline phosphatase levels. Hypercalciuria was present in 54 (31.7%) patients. Serum antinuclear antibody was positive in 21 (6.6%) patients. The majority were Tuberculin skin test (TST) negative; 89.9% of patients had induration <10 mm on TST. Two hundred and thirty-five (71.9%) were tuberculin anergic (0 mm, no induration on TST). Pulmonary hypertension was detected in 8 (6.8%) patients among the 134 who underwent echocardiography.

One hundred and fifty-six (47.7% of patients) had normal spirometry values. A possible restrictive impairment was the most common defect (146, 44.6%). Using a forced expiratory volume in 1 s/forced vital capacity cutoff of <0.70, obstruction on spirometry was observed in 25 (8.3%) patients. Nearly three-fourths of the patients (76.1%) had reduced diffusion capacity for carbon monoxide (<80% of the predicted value).

Table 1: Baseline demographic characteristics of 327 patients with sarcoidosis

| Parameter                                                                 | Value, n (%)                        |
|---------------------------------------------------------------------------|-------------------------------------|
| Age, mean±SD (minimum-maximum)                                            | 42.8±10.8 (16-70)                   |
| Males                                                                     | 166 (50.8)                          |
| Any history of smoking                                                    | 34 (10.4)                           |
| BMI kg/m² (n=319), mean±SD                                               | 25.9±4.4                            |
| Obesity (BMI >25 kg/m²) (n=319)                                            | 182 (57.1)                          |
| Any comorbidity                                                           |                                     |
| Diabetes                                                                  | 139 (42.6)                          |
| Hypothyroidism                                                            | 56 (17.1)                           |
| Hypertension                                                              | 40 (12.2)                           |
| Coronary disease                                                          | 49 (14.9)                           |
| Active malignancy                                                         | 7 (2.1)                             |
| Treated malignancy                                                        | 1 (0.3)                             |
| Connective tissue diseases                                                | 3 (0.9)                             |
| History of antitubercular treatment intake (current/previous)              | 100 (30.7)                          |
| Serum ACE level (IU/L), median (IQR) (minimum-maximum) (n=321)            |                                     |
| Elevated serum ACE level                                                  | 62 (41-95)                          |
| Blood urea (mg/dL), mean±SD (n=287)                                      | 24±10                               |
| Serum creatinine (mg/dL), mean±SD (n=287)                                 | 0.85±0.3                            |
| Calcium (mg/dL), mean±SD (n=287)                                          | 9.4±1.0                             |
| Hypercalciuria, serum calcium >11 mg/d                                    | 11 (3.8)                            |
| Serum phosphate, mean±SD (mg/dL) (n=287)                                  | 3.6±0.7                             |
| Elevated liver enzymes, (ALT >40 IU/L)                                   | 114 (34.9)                          |
| Serum ALP (IU/L), median IQR (n=280)                                     | 163.5 (102-228)                     |
| Elevated ALP (>240 IU/L)                                                 | 111 (33.9)                          |
| Urine 24-h calcium (mg) excretion, median IQR (n=170)                     | 141.75 (95-224)                     |
| Urine 24-h calcium >200 mg/24 h                                           | 54 (31.7)                           |
| Serum ANA positivity (n=247)                                              | 21 (6.6)                            |
| Serum rheumatoid factor positivity (n=255)                               | 5 (1.6)                             |
| Tuberculin skin testing induration (mm), (n=322), median (IQR), (minimum-maximum) | 0 (0-2), (0-45)                    |
| Tuberculin induration (<10 mm)                                            | 294 (89.9)                          |
| Tuberculin anergic (0 mm, no induration)                                  | 235 (71.9)                          |
| Obstructive pattern on spirometry, FEV1/FVC <70%                          | 25 (8.33)                           |
| Severity of obstruction                                                   |                                     |
| Mild to moderate (FEV1 60% or greater)                                   | 13 (52)                             |
| Moderately severe to very severe (FEV1 59% or less)                       | 12 (48)                             |
| Normal spirometry                                                         | 136 (47.7)                          |
| Possible restriction on spirometry                                        | 146 (44.6)                          |
| Reduced diffusion capacity for CO (<80% predicted)                        | 76.1                                |

BMI: Body mass index, ACE: Angiotensin-converting enzyme, ALP: Alkaline phosphatase, SD: Standard deviation, IQR: Interquartile range, ANA: Antinuclear antibodies, FVC: Forced vital capacity, FEV1: First second of forced expiration, CO: Carbon monoxide
Organ involvement and symptoms
Of the 327 patients, 167 (51%) had isolated pulmonary involvement. Nearly half (160, 49%) had involvement of an extrathoracic site. These findings are summarized in Table 2. The presence nonthoracic site lymphadenopathy (57, 17.4%), eye involvement (47, 14.4%), followed by skin involvement (36, 11.1%) were the most common sites of extrathoracic involvement. Most patients were (314, 96%) symptomatic. Cough (205, 62.7%), shortness of breath (171, 52.3%), fatigue (133, 40.7%), weight loss (119, 36.4%), and fever (104, 31.8%) were the most common symptoms. The prevalence of other symptoms is summarized in Table 2.

Table 2: Organ involvement and baseline symptoms in patients with sarcoidosis

| Parameter                                      | Value, n (%) |
|------------------------------------------------|--------------|
| Isolated pulmonary sarcoidosis                 | 167 (51)     |
| Extrapulmonary involvement                     | 160 (49)     |
| Sites of extrapulmonary involvement            |              |
| Extrathoracic lymph node                       | 57 (17.4)    |
| Eye                                            | 47 (14.4)    |
| Skin                                           | 36 (11.1)    |
| Spleen                                         | 20 (6.1)     |
| Liver                                          | 19 (5.8)     |
| Cardiac                                        | 17 (5.2)     |
| Neurological                                   | 14 (4.3)     |
| Kidney                                         | 10 (3.1)     |
| Salivary glands                                | 6 (1.8)      |
| Others                                         | 6 (1.8)      |
| Details of extrapulmonary involvement          |              |
| Uveitis                                        | 34 (10.4)    |
| Eye vasculitis                                 | 2 (0.6)      |
| Episcleritis                                   | 1 (0.3)      |
| Choroidal granulomas                           | 2 (0.6)      |
| Orbital pseudotumor                            | 2 (0.6)      |
| Abdominal/retroperitoneal lymphadenopathy      | 18 (5.5)     |
| Hepatomegaly, splenomegaly or both             | 10 (3.1)     |
| Chronic liver disease                          | 10 (3.1)     |
| Splenic lesions                                | 5 (1.5)      |
| Adrenal enlargement                            | 1 (0.3)      |
| Epididymitis                                   | 1 (0.3)      |
| Maculopapular rash                             | 16 (4.9)     |
| Erythema nodosum                               | 14 (4.3)     |
| Skin plaques                                   | 1 (0.3)      |
| Facial nerve palsy                             | 8 (2.4)      |
| Optic neuritis                                 | 3 (0.9)      |
| Peripheral neuropathy                          | 2 (0.6)      |
| Pachymeningitis                                | 2 (0.6)      |
| Peroneal nerve palsy                           | 1 (0.3)      |
| Parotid enlargement                            | 5 (1.5)      |
| Submandibular enlargement                      | 2 (0.6)      |
| Symptoms                                       |              |
| Asymptomatic                                   | 13 (4)       |
| Symptomatic                                    | 314 (96)     |
| If symptomatic, symptoms at presentation       |              |
| Cough                                          | 205 (62.7)   |
| Shortness of breath                            | 171 (52.3)   |
| Fatigue                                        | 133 (40.7)   |
| Weight loss                                    | 119 (36.4)   |
| Fever                                          | 104 (31.8)   |
| Joint pains                                    | 61 (18.7)    |
| Chest pain                                     | 44 (13.5)    |
| Visual symptoms                                | 41 (12.5)    |
| Skin changes                                   | 28 (8.6)     |
| Hemoptysis                                     | 19 (5.8)     |
| Wheezing                                       | 16 (4.9)     |
| Neurological                                   | 12 (3.7)     |
| Salivary gland enlargement                     | 7 (2.1)      |
| Lacrimal gland enlargement                     | 2 (0.6)      |

Radiological stage and imaging features
The majority of patients had Stage 1 (Scadding) (156, 47.7%) sarcoidosis followed by Stage 2 (104, 31.8%) involvement on chest radiographs. Twenty-one (6.5%) patients had normal chest radiographs. The mean lymph node short-axis diameter was 18.7 ± 7.8 mm, with a range of 6.2–56 mm [Table 3]. Subcarinal (284, 86.9%) and right lower paratracheal (283, 86.5%) were the most common lymph node stations involved. Nonhomogeneous nodes were found in 18 (5.9%) patients. Lung parenchymal involvement on CT was observed in 220 (69.4%) patients. The most common finding was the presence of lung nodules. Other findings included ground-glass opacities, cysts, traction bronchiectasis, architectural distortion, and consolidation. Honeycombing was observed in 5 (1.5%) patients. Pleural effusion was present in 18 (5.6%) patients, while an enlarged main pulmonary artery (ratio of the pulmonary artery to aortic diameter >1 at the level of bifurcation) was seen in 8 (2.5%) patients.

Diagnostic modalities and pathological investigation findings
Two hundred and eighty-seven (87.8%) patients underwent bronchoscopy or endosonography for tissue diagnosis [Table 4]. Endosonography was used in 208 (72.5%) patients. Of these, three patients underwent EUS-B-FNA, while the remaining (205) underwent EBUS-TBNA. Flexible bronchoscopy was performed in 79 (27.5%), of which 33 patients underwent conventional TBNA during the procedure. On bronchoscopic examination, endobronchial mucosal granularity was observed in 12.8% of patients. A homogeneous lymph node echotexture and absence of a coagulation necrosis sign were observed in 95.1% and 97.7% of patients, respectively, on B-mode ultrasonographic evaluation during endosonography.

A definitive diagnosis with the demonstration of granulomas was established in 297 (90.8%) patients. In the remaining patients, the diagnosis was established with a compatible clinicoradiological profile and a response to treatment over a minimum follow-up of 6 months. Tissue samples obtained during bronchoscopy or endosonography (EBUS-TBNA or EUS-B-FNA) were diagnostic in 264 (91.9%) of 287 patients who underwent the procedures. An extrathoracic lymph node biopsy was diagnostic in 24 (7.4%) patients. The diagnostic yield of EBUS-TBNA/EUS-B-FNA was 77.4%, while that of conventional TBNA was 51.5%. The diagnostic yield of TBLB and endobronchial biopsy (EBB) was 54.5% and 33.2%, respectively. Necrotizing granuloma in any tissue sample was found in 13.5%.
DISCUSSION

We have described the clinical characteristics of 327 patients of sarcoidosis, with a >90% of patients with a histopathologically confirmed diagnosis. We observed no gender predominance; there was a high prevalence of comorbidities, including obesity, a high proportion of symptomatic disease, and a low prevalence of obstructive defect on spirometry.

This paper is a large cohort study of sarcoidosis in a TB endemic setting, and we discuss the results in comparison to the previous reports in the literature. Our series had a higher percentage of biopsy-proven sarcoidosis compared to other recently published registry data. As in our cohort, previous studies have also highlighted the older age of onset of sarcoidosis in India as compared to the reports from North America, Japan, and Europe. In those settings, a bimodal distribution is described with males having an earlier onset at 30–50 years as compared to females (later onset at 50–60 years). Another difference in our series is an almost equal distribution of males and females as compared to a female predominance in the Western hemisphere. There was a high prevalence of comorbidities in our cohort, of which diabetes was most common. We also observed a high prevalence of obesity (57.1%), and the average BMI was higher than the range of Asian Indian adults. This observation is of clinical relevance as these patients may be at increased risk of steroid treatment-related adverse events. A recent study reported that metabolic syndrome is associated with increased sarcoidosis risk (7.66 relative risk).

Stage 1 involvement on chest radiographs was most common. This finding is similar to Western studies. However, in previous studies including that from tertiary care centers, Stage 2 involvement has been most commonly reported from India. On CT thorax imaging, lymph nodes showed a necrotic/nonhomogeneous appearance in 5.9% of patients. Previous studies have not described

| Parameter | n (%) |
|-----------|-------|
| Chest radiograph |       |
| Normal chest radiograph | 21 (6.5) |
| Prominent hilum | 251 (76.8) |
| Right paratracheal stripe widening | 83 (25.4) |
| Any reticular pattern or consolidation | 142 (43.4) |
| Scadding stage |       |
| Stage 0 | 21 (6.5) |
| Stage I | 156 (47.7) |
| Stage II | 104 (31.8) |
| Stage III | 42 (12.8) |
| Stage IV | 4 (1.2) |
| CT scan of the thorax |       |
| Mediastinal lymphadenopathy | 306 (94.4) |
| Lymph node size, short axis (mm), mean±SD (minimum-maximum) | 18.7±7.8 (6.2-56) |
| Enlarged lymph node stations |       |
| Subcarinal | 284 (86.9) |
| Right lower paratracheal | 283 (86.5) |
| Left paratracheal | 100 (30.6) |
| Right interlobar | 134 (40.9) |
| Left interlobar | 122 (37.3) |
| Right hilar | 246 (75.2) |
| Left hilar | 227 (69.4) |
| Right upper paratracheal | 39 (11.9) |
| Other stations | 98 (29.9) |
| Nonhomogeneous lymph node appearance | 18 (5.9) |
| Lymph node calcification | 44 (14.3) |
| Lung parenchymal involvement | 220 (69.4) |
| Lung nodules | 193 (59.6) |
| Peribronchovascular nodules | 169 (51.7) |
| Random nodules | 12 (3.7) |
| Centrilobular nodules | 20 (6.1) |
| Ground-glass opacities | 53 (16.2) |
| Honeycombing | 5 (1.5) |
| Cysts | 4 (1.2) |
| Traction bronchiectasis | 30 (9.2) |
| Architectural distortion | 23 (7) |
| Consolidation | 54 (16.5) |
| Pleural effusion | 18 (5.6) |
| Enlarged main pulmonary artery | 8 (2.5) |

CT: Computed tomography, SD: Standard deviation
the prevalence of necrosis in the lymph nodes on CT in patients of sarcoidosis. Pulmonary function tests in sarcoidosis showed an obstructive pattern in 8.3%, which is less than the reported average of about 10%–25%.[18] This difference maybe because of the different cutoffs for obstruction (80% instead of 70%) in other studies. In those patients where fluorodeoxyglucose-positron emission tomography (FDG-PET) scans were available, abdominal nodes were the most common site of extrathoracic involvement. FDG-PET-CT scanning may be useful in the assessment of disease activity, the extent of involvement, and for response assessment in active sarcoidosis.[19]

The prevalence of TST positivity (>10 mm induration, 10.1%) and tuberculin reactivity (any measurable induration, 28.1%) is greater in our cohort than previously reported.[5] A case–control study described 92% prevalence of tuberculin anergy in sarcoidosis in TB endemic population. The authors of the paper stated that tuberculin anergy in sarcoidosis is not influenced by the rate of TST positivity in the general population. The authors also concluded that a positive TST (irrespective of the size of reaction) in suspected sarcoidosis should lead to consideration of alternative diagnosis and TB.[20] However, the relevance of TST reactivity in sarcoidosis in TB endemic populations needs further exploration as the tuberculin-reactive patients in our cohort did not develop clinical TB during 6-month follow-up.

Another important observation in our study is the 13.5% prevalence of necrosis or necrotizing granulomas in biopsy samples. The presence of necrosis is commonly presumed to be diagnostic of TB by physicians in TB endemic settings. A careful review of the clinical profile and radiological and microbiological investigations was performed in patients where the tissue biopsy demonstrated necrosis. All the patients were under regular follow-up of a single pulmonologist (KM), and other conditions were ruled out by ascertaining a response to treatment and follow-up radiology. A diagnosis of sarcoidosis requires the interpretation of the clinical, radiological, and biopsy findings in conjunction rather than in isolation. A retrospective cytological study found that different patterns of granulomas do not distinguish TB from sarcoidosis.[21] Treatment decisions in granulomatous mediastinal lymphadenopathy require correlating cytologic, microbiologic, clinical, and radiological data.

The yield of EBUS TBNA (77.4%) in our study is comparable to the reported yield in a previous meta-analysis.[22] The lower yield of conventional TBNA could be contributed by the lack of rapid on-site evaluation as a routine. However, as we performed TBLB and EBB in a majority of patients, the overall diagnostic yield for procedures was good, as has been reported in previous studies with combined methods.[10,23] Our study has certain limitations. As the facility is a tertiary care and referral center, we cannot exclude a possibility of selection bias. The strengths of the study include a large sample size, a high proportion of histopathologically diagnosed patients, and a rigorous follow-up to establish a confident diagnosis. Therefore, the findings of this study likely represent a more accurate profile of sarcoidosis in TB endemic populations.

**CONCLUSION**

We have described the clinical profile of a large cohort sarcoidosis in a TB endemic population. We observed certain differences in the clinical features as compared
with the nonendemic settings. The relevance of the clinical differences on the outcomes needs further exploration.

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Conflicts of interest
There are no conflicts of interest.

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