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Calcifying fibrous tumour: An IgG4-related disease or not?

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Summary

Calcifying fibrous tumour (CFT) has some of the histopathological features, such as abundant plasma cells and stromal fibrosis, that are exhibited by IgG4-related diseases (IgG4-RD). The possible role of IgG4-positive plasma cells in calcifying fibrous tumour was investigated. The aim of this study was to determine any potential relationship between IgG4-RD and CFT. Thirteen cases with a total of 16 CFTs were reviewed. Lesion samples were immunostained with anti-IgG4 and anti-IgG antibodies. The number of IgG4-positive and IgG-positive plasma cells (IgG + PC) and their ratios were estimated. Plasma cells were found in all tumours. IgG4-positive plasma cells ranged from 0 to 71 per high-power field (HPF; mean 17.8/HPF), and IgG + PC ranged from 2 to 93/HPF (mean 42.6/HPF). The IgG4/IgG ratio ranged from 0% to 80% (mean 29%). There were seven tumours with the ratio of IgG4/IgG + PC that exceeded 40%. Various degrees of stromal fibrosis were present in eight tumours. All tumours have variable calcification. The histopathological features of CFT were found to be similar to those of IgG4-RD. Some CFT also showed a high number of IgG4-positive plasma cells, and the ratio of IgG4/IgG + PC exceeded 40%, most notably in patients with concomitant inflammatory or autoimmune disease. The long-term follow-up showed no evidence of IgG4-RD in any of these patients. Our findings suggest that while CFT overlaps morphologically with IgG4-RD, it probably should not be classified as an IgG4-RD.

KEYWORDS

calcifying fibrous tumour, IgG4-positive plasma cells, IgG4-related disease

1 | INTRODUCTION

Calcifying fibrous tumour (CFT) is a rare benign mesenchymal tumour and was first described in children's deep soft tissue by Rosenthal and Abdul-Karim as 'childhood fibrous tumour with psammoma bodies' in 1988.[1] The most common location of CFT is the abdominal cavity including the gastrointestinal tract, but it can also occurrence in soft tissues and at other visceral sites. The majority of clinical findings are asymptomatic, and CFT has been found incidentally during routine imaging examination.[1-5] Histologically, CFT is characterized by a hypocellular fibroblastic proliferation with associated chronic inflammation and variably prominent calcification as described by the World Health Organization.[6] Recently, these chronic inflammatory cells (plasma cells) were reported to be IgG4 stain positive in immunostaining studies, and thus, it has been proposed that CFT may be an IgG4-related disease (IgG4-RD).[7-10] CFT seems to share similar histopathological features with IgG4-RD, which is recognized as a

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systemic fibro-inflammatory disease characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate with many IgG4-positive plasma cells (IgG4 + PC), fibrosis and elevated serum IgG4.[11,12] The aim of the present study was to explore the possible relationship between IgG4-RD and CFTs.

2 | METHODS AND MATERIALS

With institutional review board approval, data from 13 patients with 16 CFTs were collected at a single medical centre in central Taiwan (Taichung Veterans General Hospital) from 2002 to 2018 and were retrospectively to evaluate their clinical and histopathological features. These archived formalin-fixed, paraffin-embedded tissues were immunostained with antibodies of IgG4 (MRO-44; Ventana) and IgG (polyclonal; Ventana) in Ventana Autoimmunostainer. Three high power fields (HPF; ×10 eyepiece and ×40 objective lens) of the areas with the highest density of IgG4 + PC and the corresponding areas of IgG-positive plasma cells (IgG + PC) were counted, and the average number was calculated using a microscopic system (Nikon E600) by manually counting cells in the photographs. The results were confirmed by two pathologists independently.

2.1 | Ethical approval

All experimental procedures were approved by the Ethical Committee of the Taichung Veterans General Hospital (IRB number: CE19209A).

3 | RESULTS

3.1 | Clinical features

The clinical features are summarized in Table 1. In total, there were 13 patients, with a male:female ratio of 1:1.6, and the mean age was 39.3 years (range 2-79 years). The coexisting diseases included Graves' disease, cancer, sclerosing angiomatoid nodular transformation of the spleen, inflammatory fibroid polyp, acute cholecystitis and hepatitis B virus (HBV) hepatitis. Two patients were found to have multiple tumours in different organs, and 11 patients had a solitary tumour. The involved sites included the GI tract (n = 7), peritoneum (n = 4), chest cavity (n = 3), genitourinary system (n = 1) and back soft tissue (n = 1). Tumours ranged from 5 to 260 mm (median 39.6 mm). Most CFTs were identified incidentally during a healthy examination or unrelated surgical procedures (n = 8). The other cases presented with foreign body sensation in the throat, hydronephrosis, constipation and abdominal pain. Serum IgG4 and IgG concentrations were not measured in any of the patients, and no patients had been diagnosed with an IgG4-RD during follow-up, which ranged in duration between 0 and 36 months (median 5.4 months).

3.2 | Pathologic features

The pathological features of the tumours are summarized in Table 2. A review of histological revealed that tumours were well-circumscribed, had hypocellular spindle cell proliferations with abundant hyalinized collagen and were mostly arranged haphazardly. A focal storiform pattern of fibrosis was noted in many cases (n = 8; Figure 1A). All tumours have variable calcification, and the pattern of calcification varied from dystrophic (n = 15; Figure 1B), psammomatous (n = 11; Figure 1C), lamellar bone formation (n = 2; Figure 1D), to mixed pattern (n = 12). All tumours had associated lymphoplasmacytic inflammatory infiltrates. The lymphoplasmacytic infiltrate was mostly in the form of lymphoid aggregates with or without germinal centres (n = 11; Figure 1E), and the others were sparsely scattered throughout the lesion (n = 5; Figure 1F). No obliterative phlebitis was found in any of the tumours.

3.3 | Immunohistochemistry

The numbers of IgG4 + PC and IgG + PC and their ratios are listed in Table 2. IgG + PC was detected in all of the cases of CFTs, and five cases showed no IgG4 + PC. On average, the number of IgG4 + PC and IgG + PC ranged from 0 to 71/HPF (mean, 17.8/HPF) and from 2 to 93/HPF (mean, 42.6/HPF), respectively. The IgG4 + PC/IgG + PC ratio ranged from 0% to 80% (mean, 29%). There were seven tumours with a ratio of IgG4 + PC/IgG + PC that exceeded 40%. Ratio of 44%, 60% and 80% are representatively presented in the Figure 2A-F.

3.4 | Clinical-pathological correlations

Seven tumours had a IgG4 + PC/IgG + PC ratio that exceeded more than 40%. All of the cases exhibited lymphoplasmacytic infiltration, and 8 of the tumours had the storiform pattern of fibrosis. No obliterative phlebitis was found in any of the cases. There was a slight female predominance and CFT usually coexisted with an inflammatory or autoimmune-like disease, such as Graves' disease, inflammatory fibroid polyp, acute cholecystitis and HBV hepatitis. None of the patients were diagnosed with an IgG4-related systemic disease during follow-up.

TABLE 1 Summary of clinical features

Case no.	Sex	Age	Size (mm)	Number of tumour	Location	Coexisting disease	Clinical presentation	Follow-up/ mo	Outcome
1	F	2	25	1	Soft tissue of back	None	Incidental finding	Lose follow-up	Disease free
2	F	24	50	1	Mediastinum	None	Incidental finding	27	Disease free
3	F	54	30	1	Oesophagus	None	Foreign body sensation over throat for a period of time	1	Disease free
4	F	26	260	1	Peritoneum (near ovary)	None	Palpable abdominal mass for more than 10 y	0.5	Disease free
5	F	28	52	1	Small intestine	Grave's disease, s/p partial thyroidectomy and thyroidectomy related hypothyroidism, under thyroxine supplement	Incidental finding at C/S	2	Disease free
6	M	38	45 10	2	Small intestine (ileum)	Inflammatory fibroid polyp (IFP) of ileum	Intermittent abdominal pain over epigastric and periumbilical area for 3 mo	1 Lose follow-up	Disease free Unknown
7	F	40	13 32 8	3	Stomach Peritoneum Peritoneum	Splenic tumour (sclerosing angiomatoid nodular transformation)	Left side low back pain for 5 y	0.5	Disease free
8	M	76	5	1	Small intestine	(a) Bladder cancer s/p TURP in 1994 and chemotherapy, (b) Colon cancer	Incidental finding at operation for colon cancer	36	Disease free
9	M	13	35	1	Chest wall	None	Incidental finding at healthy exam	0.5	Disease free
10	F	78	5	1	Small intestine	Colon cancer s/p laparoscopic anterior resection	Incidental finding at operation for colon cancer recurrent	0.5	Disease free
11	F	79	15	1	Peritoneum	Gallstones with acute cholecystitis	Incidental finding at operation	0.5	Disease free
12	M	27	18	1	Spermatic cord	None	Scrotum enlargement for 4 y	lose follow-up	Unknown
13	M	26	30	1	Subpleural	HBV hepatitis	Incidental finding at healthy examination	0.5	Disease free

4 | DISCUSSION

Calcifying fibrous tumour is a rare benign tumour and characterized by hypocellular fibroblastic proliferation, chronic inflammation and calcification.[1-6] Sixteen tumours occurred in 13 cases were collected in a period of 16 years. Our results show slightly female predominance, more in young adult and child, and GI tract is the most common involved site though the anatomic distribution is wide. These findings are similar to the previous literature.[2] The diagnosis of IgG4-RD is based on the combination of characteristic histopathological, clinical, serologic and radiologic findings. The characteristic histopathological features include lymphoplasmacytic tissue infiltration of mainly IgG4-positive plasma cells and lymphocytes, accompanied by storiform fibrosis and often by obliterative phlebitis.[11,12] The triad of morphologic findings in CFT is central to raising suspicion for IgG4-RD. Also, based on observations in CFT case reports that tumour tissue contained a high amount of IgG4 + PC, some authors have recently hypothesized that CFT could be an IgG4-RD.[7-10]

TABLE 2 Summary of pathological features

NO	Whorled pattern	Lymphoid aggregation	Psammoma body (round)	Dystrophic calcification (irregular shape)	Lamella bone formation	Plasma cells	Number of IgG4 + PC/ HPF (mean/3 hpf)	Number of IgG + PC/HPF (mean/3 hpf)	IgG4 + PC/ IgG + PC ratio
1	N	Y	N	Y	N	+	3	30	0.1
2	Y	Y	Y	Y	N	++	24	40	0.6
3	Y	Y	Y	Y	N	++	20	45	0.44
4	N	N	N	Y	Y	+	0	3	0.00
5	Y	N	Y	Y	N	+	5	11	0.45
6	N	Y	N	Y	N	+++	71	89	0.80
	N	Y	Y	Y	N	+++	64	80	0.80
7	Y	Y	Y	N	N	+	8	53	0.15
	N	Y	N	Y	Y	+	0	20	0.00
	N	N	Y	Y	N	+	0	20	0.00
8	N	Y	N	Y	N	+	0	2	0.00
9	Y	Y	Y	Y	N	++	39	93	0.42
10	N	N	Y	Y	N	+	0	10	0.00
11	Y	N	Y	Y	N	+	3	66	0.05
12	Y	Y	Y	Y	N	++	19	56	0.34
13	Y	Y	Y	Y	N	++	28	64	0.44

Abbreviations: +, few; ++, moderate; +++, many; IgC + PC, IgG-positive plasma cells; IgG4 + PC, IgG4-positive plasma cells; N, absent; Y, present.

Our analysis of the histological and clinical features of 16 CFT in 13 patients revealed that CFT commonly showed dense lymphoplasmacytic infiltration, storiform fibrosis and IgG4 + PC infiltration, suggesting that a certain proportion of tumours (~44%) share histological features with IgG4-RD. However, some features of CFT did not exhibit classical features of IgG4RD, such as the third feature of the triad, obliterative phlebitis, has never been documented in CFT,[2-6] and our results were consistent with this observation.

From a clinical perspective, response to corticosteroid therapy is also highly suggestive of IgG4-RD, and there are no reports in the literature describing treatment of CFT with steroids.[2,11,12] Surgical excision is the main treatment for patients with CFT.[2,3] Patients with IgG4-RD lesions can also present with synchronous or metachronous other-organ involvement, and IgG4-RD lesions may also recur after surgery, while CFT has rarely been noted to recur locally, and there has never been a report of metastasis.[2] In our study, no involvement of other organs, tumour recurrence or tumour metastasis was noted in any of our CFT patients, and during follow-up, none of the patients developed a systemic disease.

Elevations in tissue IgG4 concentrations are not specific to IgG4-RD and can be found in a wide variety of non-IgG4-RD disorders, such as inflammatory conditions, lymphoma, malignancy and a large number of other conditions. Inflammatory disease conditions potentially associated with an increased number of IgG4 + PC include oral inflammatory diseases, primary sclerosing cholangitis, anti-neutrophil cytoplasmic antibody-associated vasculitis, rheumatoid arthritis, inflammatory bowel disease, rhinosinusitis, Rosai-Dorfman disease, splenic sclerosing angiomatoid nodular transformation, cutaneous plasmacytosis, perforating collagenosis, autoimmune atrophic gastritis (pernicious anaemia), pulmonary abscess, biliary xanthogranulomatous inflammation and lymphoproliferative disorders such as multicentric Castleman's disease.[7,13-19] IgG4 + plasma cells are known to be capable of infiltrating cancer tissue, although the extent of infiltration varies. Most studies on this phenomenon were investigations of pancreatobiliary cancers, but it has also been observed in other malignancies.[20,21] While IgG4 + plasma cells have been detected in the regional lymph nodes of cancer patients, the precise frequency of occurrence and the underlying mechanism remains unclear.[22]

Likewise, elevated serum levels of IgG4 are not found only in IgG4-RD. Culver et al collected 2067 samples from 1510 patients. Among patients whose final diagnosis did not met the criteria of IgG4-RD, but who had increased serum IgG4 levels, the following conditions and diseases were noted: malignancy, primary sclerosing cholangitis, pancreatitis, cirrhosis, autoimmune hepatitis, inflammatory bowel disease, autoimmune disease, hepatitis, biliary disease, gallstones, overlap primary sclerosing cholangitis/autoimmune hepatitis, primary biliary cholangitis and drug-induced elevation of IgG4.[23]

This may explain why the IgG4 + PC in CFT rise in patients with a coexisting disease. The coexisting diseases in our data included Graves' disease, inflammatory fibroid polyp and HBV hepatitis. There are no reported cases of CFT

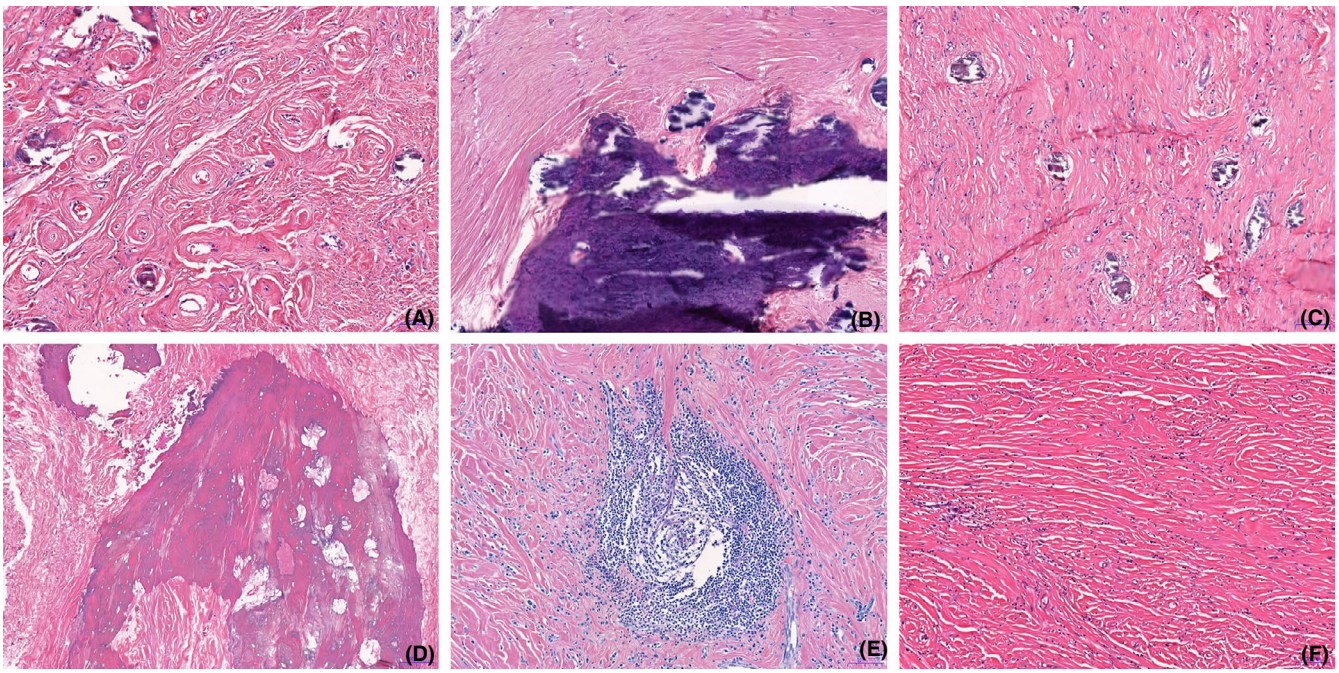

FIGURE 1 A, Storiform pattern of fibrosis (100×); B, dystrophic calcification (100×); C, psammomatous calcification (100×); D, lamellar bone formation (100×); E, lymphoid aggregation with germinal centre (100×) and F, lymphocytes scattered infiltration (100×)

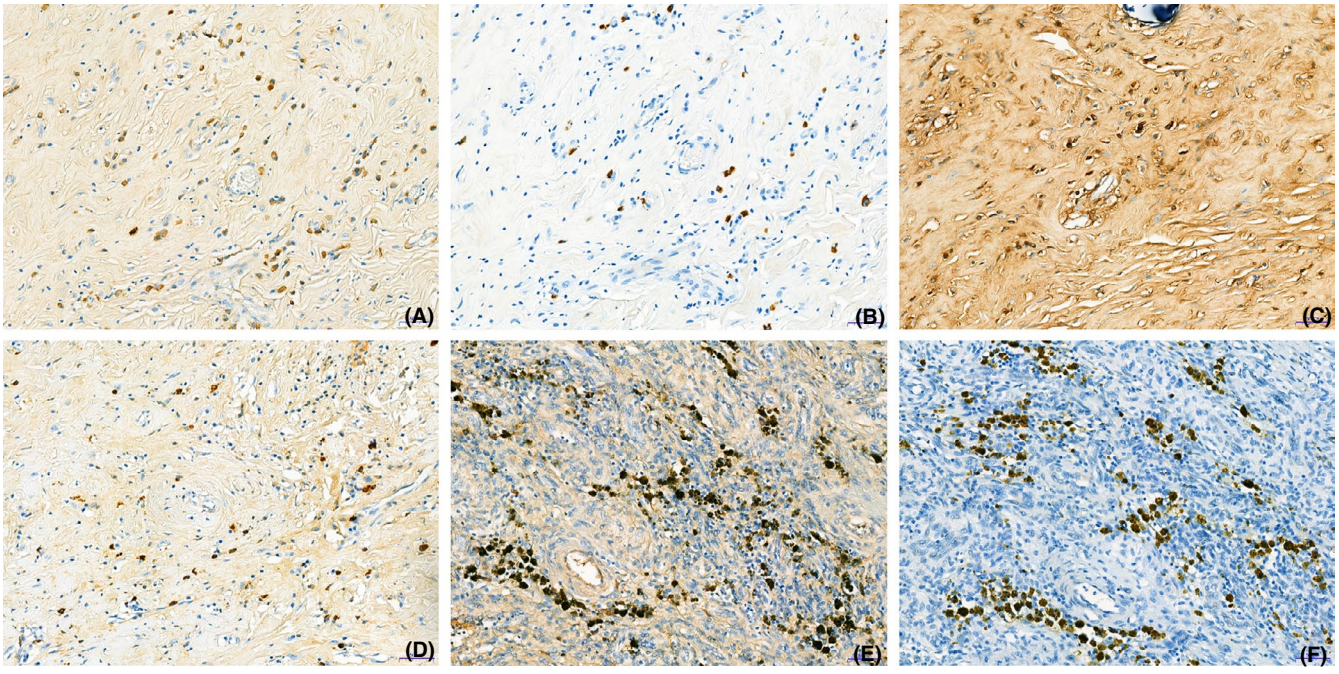

FIGURE 2 IHC stains for IgG + PC and IgG4 + PC in CFT with the IgG + PC/ IgG4 + PC ratio exceeded 40% in three samples. A, IgG + PC; B, IgG4 + PC, the ratio of IgG4 + PC/IgG + PC was 44%; C, IgG + PC; D, IgG4 + PC, the ratio of IgG4 + PC/IgG + PC was 60%; E, IgG + PC and F, IgG4 + PC, the ratio of IgG4 + PC/IgG + PC was 80%. All at 200×. IgC + PC, IgG-positive plasma cells; IgG4 + PC, IgG4-positive plasma cells

coexisting with a known IgG4-RD, such as autoimmune pancreatitis, but CFT has been documented to coexist in patients with other rare tumefactive lesions, including hyaline-vascular type Castleman disease, and sclerosing angiomatoid nodular transformation of the spleen.[7,24-26] Though none of any entities is currently recognized as an IgG4-RD, like CFTs, they do share some common features. A study conducted by Kuo et al[7] showed an association of sclerosing angiomatoid nodular transformation of the spleen and CFT in five patients, and all of these cases had a clear preponderance of

IgG4 + PC in their inflammatory infiltrates. However, in our study, one of the cases (7th case) had sclerosing angiomatoid nodular transformation of the spleen, with only very limited IgG4 + PC infiltration (0-8 IgG4 + PC/HPF), and the ratio of IgG4 and IgG was 0%-15%, much less than 40%.

One of the patients in our collected data had HBV hepatitis. In one study on HBV hepatitis, there was an association between IgG4 levels and higher rates of viral replication, which implies that IgG4 may enhance infectivity. This evidence was used to suggest that IgG4 may have a crucial role in hepatic-fibrogenic driving forces in HBV patients.[27] Graves' disease, which is characterized by hyperthyroidism, was another coexisting disease that was found in one of our patients. A small subset of patients with Graves' disease have been found to have elevated serum IgG4 levels. These patients were older and had more hypo-echoic areas on ultrasonography, but histological differences were not evaluated.[28] An association of Graves' ophthalmopathy with elevated serum IgG4 levels has also been found,[29] but more data are required to definitively link this to IgG4-RD.

There were some limitations in our study. First, preoperative and postoperative serum IgG4 levels were not evaluated in our patients. Serum IgG4 levels should be measured, and elevated levels are a significant aid in the diagnosis of IgG4-RD, although they are not diagnostic alone, because serum IgG4 concentrations are neither sufficiently sensitive nor specific for this disease and may not reflect tissue levels.[11,12] There are only two case reports in CFT which include data about serum IgG4 levels. Zhang et al[10] reported a gastric CFT in a 55-year-old woman; the serum IgG4 level was 169 mg/dL, and, this patient had coexisting autoimmune diseases, including autoimmune atrophic gastritis, Hashimoto's thyroiditis and possible primary biliary cirrhosis. These autoimmune diseases may contribute to the elevated serum IgG4 level as we have already known. Larson et al[9] reported an ileal CFT in a 42-year-old man, underwent segmental resection with unknown serum IgG4 level. He was found to have an elevated serum IgG4 level of 185 mg/dL, 3 months postremoval of the CFT, during serology examination for acute peritonitis. The elevated IgG4 may be due to the inflammatory process and unrelated to the CFT. Second, only 13 patients (16 tumours) were identified in our hospital records, and there were numerous involved organs, and so, no specific organ system could be classified. Further studies with a higher number of patients and collection of serum data are recommended in order to obtain a clearer understanding of the clinicopathological correlation between CFT and IgG4-RD.

5 | CONCLUSION

The histopathological features of CFTs, such as the constant presence of plasma cells with prominent stromal sclerosis, are similar to those of IgG4-RD. Some CFTs also showed a high number of IgG4 + PC, and the ratio of IgG4 + PC/IgG + PC exceeded 40%, especially in patient with as coexisting inflammatory or autoimmune disease. The long-term follow-up showed no evidence of IgG4-RD in any of our patients. Our findings suggest that while CFT overlaps morphologically with IgG4-RD, it probably should not be classified as an IgG4-RD.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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