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【 CASE REPORT 】

The "Ant-farm"-like Appearance of Restricted Lower Limb Vasculitis on Fluorodeoxyglucose-positron Emission Tomography

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Abstract:
Restricted lower limb vasculitis is a type of localized muscle vasculitis limited to the lower limbs. The usefulness of fluorodeoxyglucose-positron emission tomography (FDG-PET) for the diagnosis of this entity has not yet been reported. We herein report three patients with a fever and persistent lower limb pain. FDG-PET revealed linear and patchy FDG uptakes in their lower limbs. Combined with magnetic resonance imaging and histological findings, they were diagnosed with lower limb vasculitis. Linear and patchy FDG uptakes are considered to reflect the presence of muscle vasculitis. The characteristic "ant-farm"-like FDG-PET images can be a diagnostic clue for the currently overlooked vasculitis.

Key words: restricted lower limb vasculitis, muscle vasculitis, FDG-PET, fever, myalgia

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Introduction

Systemic vasculitis affects multiple organs and includes various forms of vasculitis, such as giant cell arteritis, Takayasu arteritis, polyarteritis nodosa, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. In contrast, localized vasculitis involves a single organ, such as the kidney, lungs, or auris media (1). Muscles, especially in the lower limbs, have been reported to be target organs for localized vasculitis (1). Muscle vasculitis limited to the lower limbs has been referred to as restricted lower limb vasculitis (2-5). However, this disease is yet to be widely recognized, and effective diagnostic methods have not been established.

Most previously reported cases were diagnosed based on histology and magnetic resonance imaging (MRI) of the affected muscles. The usefulness of fluorodeoxyglucose-positron emission tomography (FDG-PET) for diagnosing restricted lower limb vasculitis has not been reported, despite its well-established diagnostic utility for large-vessel vasculitis (6, 7).

We herein report three cases of restricted lower limb vasculitis in which FDG-PET revealed characteristic findings contributing towards its diagnosis.

Case Reports

Case 1

A 71-year-old Japanese man was admitted to our hospital due to a fever and persistent pain in the lower limbs that had developed 2 months earlier. His body temperature was 38.7 ℃, and the patient had severe tenderness in his thighs and calves. He had slight muscle weakness in the proximal and distal part of his legs. Blood tests revealed a C-reactive protein (CRP) level of 26.99 mg/dL and normal creatine kinase, myoglobin, and aldolase levels. Autoantibodies, including antinuclear antibody, rheumatoid factor, anti-cyclic citrullinated peptide antibody, anti-SSA antibody, ANCA,

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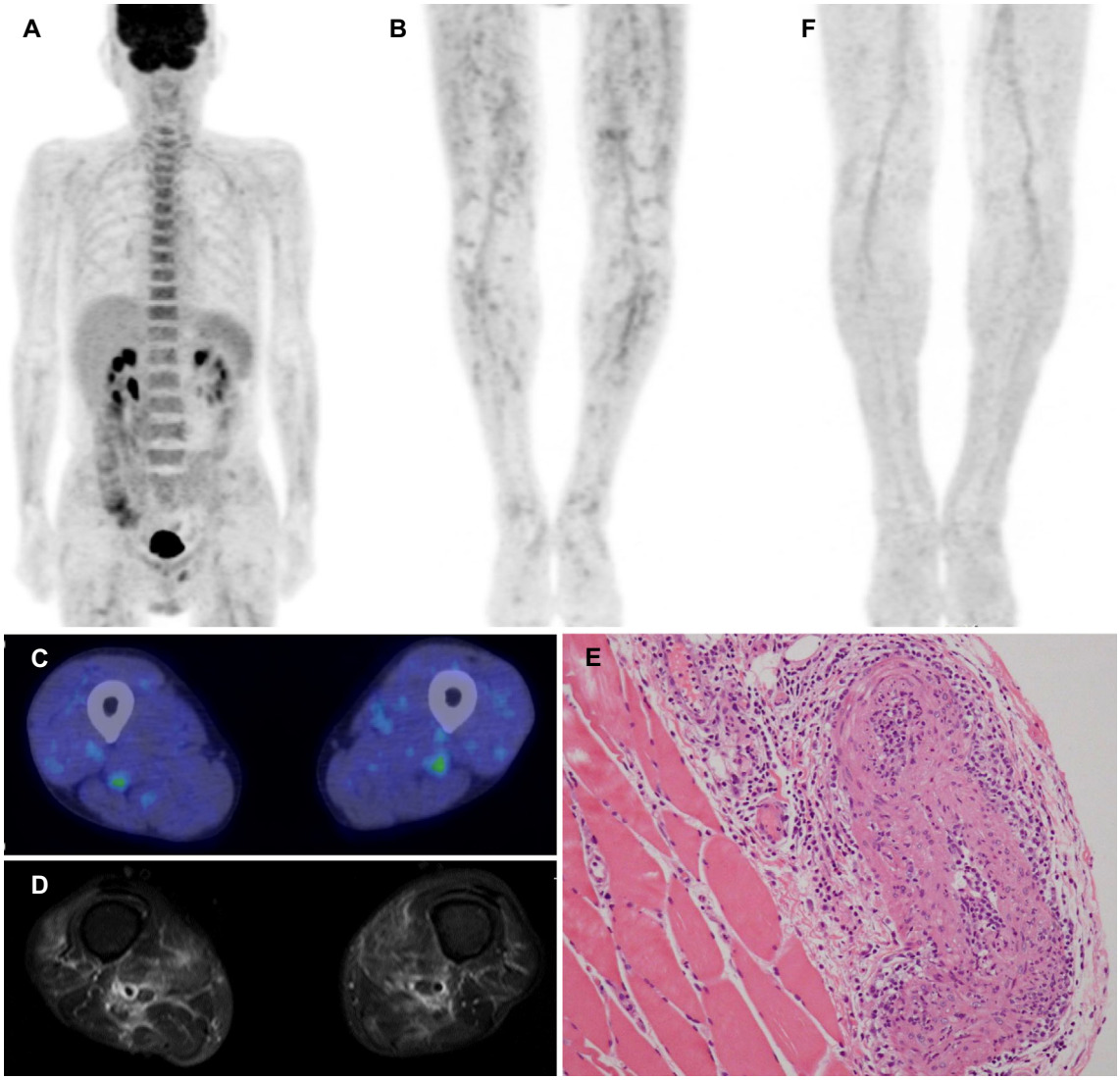

Figure 1. **Clinical findings of case 1. (A-C) Fluorodeoxyglucose-positron emission tomography (FDG-PET) findings at the first evaluation. No significant FDG uptake was observed in the trunk or upper limbs (A), while a linear and patchy uptake was detected in the lower limbs (B). (C) FDG-PET/computed tomography in the thighs showed an increased FDG uptake in the femoral arteries. (D) Magnetic resonance imaging with a short T1 inversion recovery sequence revealed a high intensity in the artery wall and perivascular connective tissues. (E) Hematoxylin and Eosin staining image of the muscle biopsy specimen obtained from the right vastus lateralis muscle (×200). A vasculitis composed of fibrinoid necrosis and infiltration of inflammatory cells in the arterial walls was noted. (F) FDG-PET showed the significant resolution of the patchy uptake in the lower limbs after treatment.**

and anti-aminoacyl-tRNA synthetase antibody, were negative.

FDG-PET revealed a linear and patchy FDG uptake in the lower limbs, without a significant uptake in the trunk or upper limbs (Fig. 1A-C). MRI of the thighs showed a high intensity in the artery wall and perivascular connective tissues (Fig. 1D). A histological analysis of a muscle biopsy specimen from the right vastus lateralis muscle revealed vasculitis composed of fibrinoid necrosis and infiltration of inflammatory cells in the arterial walls (Fig. 1E).

The patient was diagnosed with restricted lower limb vasculitis. Prednisolone was administered orally at an initial dosage of 40 mg/day (0.8 mg/kg/day), after which the patient gradually defervesced, the pain in the lower limbs decreased, and the serum CRP level returned to a normal range. Follow-up FDG-PET performed eight months later showed significant resolution of aberrant FDG uptake (Fig. 1F).

Case 2

A 73-year-old Japanese man was admitted to our hospital due to fever and persistent pain in the left thigh that had developed one month earlier. On presentation, his body temperature was 37.8 ℃. Physical examination of the muscles revealed severe tenderness in the left thigh, with moderate tenderness in the right thigh and calves. No apparent weak-

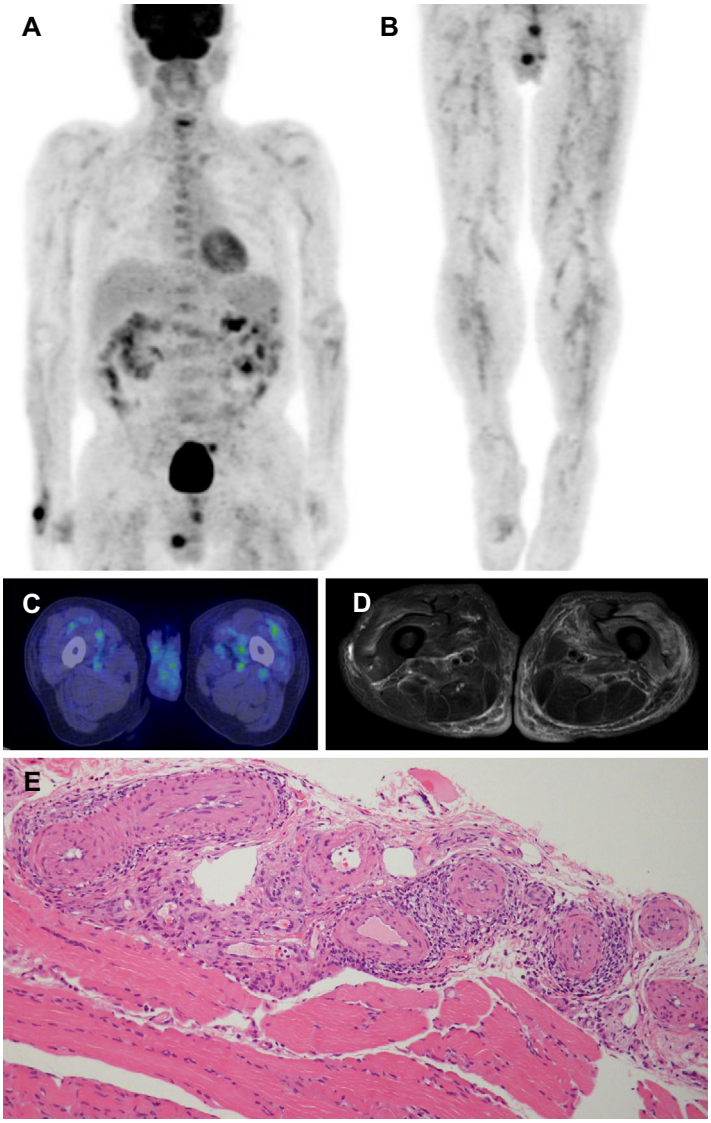

Figure 2. **Clinical findings of Case 2. (A-C) The F-18 fluorodeoxyglucose-positron emission tomography (FDG-PET) image in the first evaluation. There is no significant FDG uptake in the trunk and upper limbs (A), while a linear and patchy uptake was detected in the lower limbs (B). (C) FDG-PET/computed tomography in the thighs showed an increased FDG uptake in the femoral arteries. (D) Magnetic resonance imaging with a short T1 inversion recovery sequence revealed muscle edema, especially in the left thigh muscle. (E) Hematoxylin and eosin staining image of the muscle biopsy specimen obtained from the left vastus lateralis muscle (×200). Infiltration of inflammatory cells in the arterial walls was noted without fibrinoid necrosis.**

ness in the muscles was observed. Serum CRP level was 17.83 mg/dL, muscle enzyme levels were normal, and autoantibodies, including ANCA, were negative. The FDG-PET images demonstrated linear and patchy uptake in the lower limbs without significant uptake in the trunk and upper limbs (Fig. 2A-C). The left thigh showed slightly stronger FDG uptake, which was consistent with severe pain predominantly in the left side (Fig. 2C). MRI of the thighs revealed muscle edema, especially in the left thigh muscle (Fig. 2D). Histological analysis of a muscle biopsy specimen from the left vastus lateralis muscle showed infiltration of inflammatory cells in the arterial walls (Fig. 2E).

The patient was diagnosed with restricted lower limb vasculitis. Prednisolone was administered orally at an initial dosage of 20 mg/day (0.4 mg/kg). In response to the treatment, fever and lower limb pain gradually improved, and serum CRP level decreased to a normal range.

Case 3

An 86-year-old Japanese man was admitted to our hospital due to fever and persistent lower limb pain that had developed one month earlier. On presentation, his body temperature was 38.4 ℃. A physical examination of his muscles revealed severe tenderness in his thighs and calves, with slight muscle weakness in the proximal and distal muscles of the legs. The CRP level was 17.29 mg/dL, the muscle en-

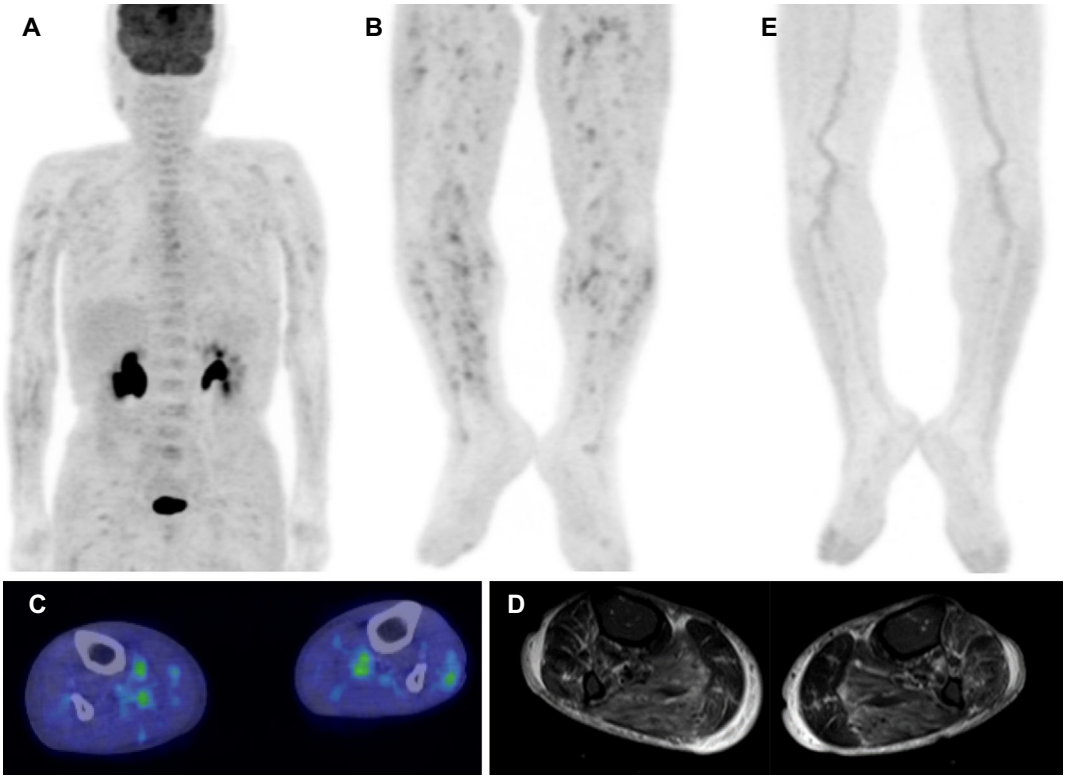

Figure 3. **Clinical findings of Case 3. (A-C) Fluorodeoxyglucose-positron emission tomography (FDG-PET) findings at the first evaluation. No significant FDG uptake was observed in the trunk or upper limbs (A), while multiple patchy uptakes in the lower limbs were noted (B). (C) FDG-PET/computed tomography in the thighs showed an increased FDG uptake in the crural muscles. (D) Magnetic resonance imaging with a short T1 inversion recovery sequence revealed a diffuse high intensity in the femoral muscles. (E) FDG-PET showed the significant resolution of the patchy uptake in the lower limbs after treatment.**

zyme levels were normal, and all autoantibodies, including ANCA, were negative.

FDG-PET demonstrated a linear and patchy uptake in the lower limbs and no significant uptake in the trunk and upper limbs (Fig. 3A-C). MRI of the lower legs revealed diffuse muscle edema (Fig. 3D). A muscle biopsy could not be performed because of severe hypoalbuminemia.

The patient was clinically diagnosed with restricted lower limb vasculitis. Prednisolone was administered orally at an initial dosage of 30 mg/day (0.8 mg/kg/day). In response to the treatment, the patient's fever and lower limb tenderness promptly improved, and the serum CRP level decreased to a normal range. Follow-up FDG-PET performed 10 months later showed significant resolution of the previously observed patchy FDG uptake (Fig. 3E).

Discussion

In this case series, we presented three cases of restricted lower limb vasculitis. FDG-PET of the limbs revealed a linear and patchy FDG uptake pattern, which we named an "ant-farm"-like appearance, after its distinctive shape, as described later. The findings from these three cases suggest that FDG-PET can help in the diagnosis of restricted lower limb vasculitis (Table).

Restricted lower limb vasculitis has been diagnosed by histology and MRI in previous reports. Histological analyses of the affected muscles revealed leukocyte infiltration into the vessel walls (4). These findings are distinct from those of inflammatory myositis, which is characterized by necrosis or inflammatory destruction of muscle fibers (5). Thus, restricted lower limb vasculitis has a different etiology from that of inflammatory myositis. In addition to histology, MRI has also been used to detect restricted lower limb vasculitis. Vasculitis in the muscles is visualized as hyperintense T2 signals and slow short T1 inversion recovery sequences (2). The MRI findings are applied to an auxiliary diagnosis and utilized to determine an appropriate site for a muscle biopsy (2, 3). In our patients, histological analyses revealed edematous changes in the muscle caused by the infiltration of inflammatory cells in the arterial walls in Cases 1 and 2, which coincides with the previously reported findings of muscular vasculitis (5). In addition, the MRI findings of the three patients were compatible with those of vasculitis in the muscles.

FDG-PET is a functional imaging technique that is established for oncology, and its utility for identifying the presence and disease activity of large-vessel vasculitis (giant cell

Table. Clinical Features and Laboratory Findings in Our Cases.

Case	Age (yr), sex	Myalgia	Muscle weakness	CRP (mg/dL)	Muscle enzymes	Autoantibodies	MRI findings		Muscle biopsy		PET-CT findings	Initial therapy
							Thigh	Calf	Portion	Histology		
1	71, M	Bilateral thighs and calves	Proximal and distal legs	26.99	Normal	Negative	Positive	N/A	Right vastus lateralis	Vasculitis	Linear and patchy FDG uptake in the lower limbs	Prednisolone 40 mg/day
2	73, M	Bilateral thighs and calves	None	17.83	Normal	Negative	Positive	N/A	Left vastus lateralis	Vasculitis	Linear and patchy FDG uptake in the lower limbs	Prednisolone 20 mg/day
3	86, M	Bilateral thighs and calves	Proximal and distal legs	17.29	Normal	Negative	N/A	Positive	N/A	N/A	Linear and patchy FDG uptake in the lower limbs	Prednisolone 30 mg/day

yr: year, M: male, CRP: C-reactive protein, MRI: magnetic resonance imaging, N/A=not available, PET-CT: positron emission tomography-computed tomography, FDG: F-18 fluorodeoxyglucose

arteritis and Takayasu arteritis) has recently been recognized (6, 7). In our cases, we suspected vasculitis based on the clinical presentation (Table). FDG-PET revealed an aberrant FDG uptake in the lower limbs, findings that were distinct from those of inflammatory myositis and large-vessel arteritis. Typical PET findings include a diffuse uptake in the affected muscle in inflammatory myositis (8) and an increased uptake along with vascular walls in large-vessel arteritis (9). The linear and patchy FDG uptake in our cases reflects muscular vasculitis. Indeed, the presence of muscular vasculitis in Cases 1 and 2 was confirmed by a muscle biopsy (Table). Although a muscle biopsy was not performed for Case 3, the presence of vasculitis is strongly suggested in muscle tissues, as the MRI and FDG-PET findings were similar to those of Cases 1 and 2, and the aberrant PET findings disappeared after steroid treatment. Of note, FDG-PET of the limbs revealed a characteristic FDG uptake pattern. The linear and patchy FDG uptake appears to reflect the inflammation of medium-sized blood vessels and nodular small-sized vasculitis in the muscles, respectively. Since the distinctive shape is similar to that of an ant farm (a colony of ants in a glass-sided dirt-filled box), we named this linear and patchy FDG uptake an “ant-farm”-like appearance.

Interestingly, in our cases, muscle vasculitis was restricted to the lower limbs. Similar localized muscle vasculitis has been reported in several case reports and is referred to as restricted lower limb vasculitis (3). It has been previously reported that the most frequently involved muscles are those in the calf (3). The pathological process is confined to the vessels supplying the lower limb muscles, and there is reportedly no clinical or instrumental evidence of systemic involvement (4). In our cases, FDG-PET clearly revealed the absence of involvement of other organs. The detailed mechanisms by which vasculitis is limited to the lower limbs remain unclear. In addition, whether or not restricted lower limb vasculitis progresses to systemic vasculitis with organ involvement is also unclear. The accumulation of similar cases and detailed analyses of clinical and imaging findings are required to better understand and manage this disease.

Making a diagnosis of restricted lower limb vasculitis is challenging because of the lack of information on accurate clinical and laboratory markers, such as muscle enzyme levels that are either normal or very slightly increased (2). Consequently, restricted lower limb vasculitis can present as a fever of unknown origin before its definite diagnosis (4). Our cases illustrated that FDG-PET is useful for detecting the presence and activity of restricted lower limb vasculitis. To our knowledge, there have been no previous reports demonstrating the usefulness of FDG-PET in diagnosing restricted lower limb vasculitis. Although there are a few case reports of polyarteritis nodosa showing a similar patchy FDG uptake to the present cases (10-12), the findings were not restricted to the lower limbs, and the presence of vasculitis was not confirmed histologically. There seem to be three possible reasons as to why the FDG-PET findings of restricted lower limb vasculitis have not been reported thus far: 1) the uptake in the lower limbs is overlooked as a nonspecific finding, 2) FDG-PET is not often performed because of its high cost, and 3) the lower limbs are not routinely imaged, especially when there are no noticeable symptoms in the lower limbs. Although the gold standard for diagnosing muscle vasculitis is a biopsy (2), a muscle biopsy can be false negative by 33.3% for muscular involvement of vasculitis (13). Furthermore, accompanying hypoalbuminemia due to a chronic inflammatory status often limits the indication of a muscle biopsy (14). Therefore, we would like to emphasize the usefulness of FDG-PET for detecting restricted lower limb vasculitis non-invasively in patients with lower limb pain and a fever of unknown origin. By performing FDG-PET in addition to a muscle biopsy or MRI, an early and accurate diagnosis of restricted lower limb vasculitis can be achieved.

Recently, diffusion-weighted whole-body imaging with background body signal suppression (DWIBS) has been reported to be useful in the evaluation of disease activity in

large-vessel vasculitis (15, 16). DWIBS has some advantages over FDG-PET, such as no radiation exposure and a low cost. As there have been only a limited number of reported cases in which DWIBS has been applied to small- or medium-vessel arteritis, the clinical usefulness of DWIBS in restrictive lower-extremity vasculitis needs to be clarified through further analyses. In addition, the usefulness of other imaging tools, such as contrast-enhanced computed tomography and angiography, for restricted lower limb vasculitis also needs to be evaluated. Further imaging characterization with more accessible imaging tools than FDG-PET and MRI will be required to diagnose such cases properly in community hospitals.

In conclusion, this is the first report describing the unique PET findings of restricted lower limb vasculitis and its usefulness in diagnosing the disease. Because restricted lower limb vasculitis is not widely recognized, it is often overlooked. Clinicians should consider the possibility of restricted lower limb vasculitis in patients with persistent lower limb pain associated with a high inflammatory state. The characteristic "ant-farm"-like FDG-PET findings in the lower limbs are a diagnostic clue for otherwise overlooked vasculitis.

The patients provided their written consent for the publication of this case reports, including copies of their clinical imaging results.

The authors state that they have no Conflict of Interest (COI).

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