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^{18}F-FDG PET/CT as a central tool in the shift from chronic Q fever to *Coxiella burnetii* persistent focalized infection

A consecutive case series

Carole Eldin, MD[a], Cléa Melenotte, MD[a], Matthieu Million, MD, PhD[a], Serge Cammilleri, MD, PhD[b], Albert Sotto, MD[c], Antoine Elsendoorn, MD[d], Franck Thuny, MD, PhD[a,e], Hubert Lepidi, MD, PhD[a], France Roblot, MD, PhD[f], Thierry Weitten, MD[g], Souad Assaad, MD[h], Anissa Bouaziz, MD[i], Claire Chapuzet, MD[j], Guillaume Gras, MD[k], Anne-Sophie Labussiere, MD[l], Cécile Landais, MD[m], Pascale Longuet, MD[n], Agathe Masseau, MD[o], Olivier Mundler, MD, PhD[b], Didier Raoult, MD, PhD[a,*]

Abstract

Because Q fever is mostly diagnosed serologically, localizing a persistent focus of *Coxiella burnetii* infection can be challenging. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) could be an interesting tool in this context.

We performed a retrospective study on patients diagnosed with *C burnetii* infection, who had undergone ^{18}F-FDG PET/CT between 2009 and 2015. When positive ^{18}F-FDG PET/CT results were obtained, we tried to determine if it changed the previous diagnosis by discovering or confirming a suspected focus of *C burnetii* infection.

One hundred sixty-seven patients benefited from ^{18}F-FDG PET/CT. The most frequent clinical subgroup before ^{18}F-FDG PET/CT was patients with no identified focus of infection, despite high IgG1 serological titers (34%). For 59% (n = 99) of patients, a hypermetabolic focus was identified. For 62 patients (62.6%), the positive ^{18}F-FDG PET/CT allowed the diagnosis to be changed. For 24 of them, (38.7%), a previously unsuspected focus of infection was discovered. Forty-two (42%) positive patients had more than 1 hypermetabolic focus. We observed 21 valvular foci, 34 vascular foci, and a high proportion of osteoarticular localizations (n = 21). We also observed lymphadenitis (n = 27), bone marrow hypermetabolism (n = 11), and 9 pulmonary localizations.

We confirmed that ^{18}F-FDG PET/CT is a central tool in the diagnosis of *C burnetii* focalized persistent infection. We proposed new diagnostic scores for 2 main clinical entities identified using ^{18}F-FDG PET/CT: osteoarticular persistent infections and lymphadenitis.

Abbreviations: ^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, *C burnetii* = *Coxiella burnetii*.

Keywords: ^{18}F-FDG PET/CT, *Coxiella burnetii*, diagnosis, focalized persistent infection, Q fever

1. Introduction

Q fever is a worldwide zoonosis caused by the bacterium *Coxiella burnetii*. Since the first studies on Q fever, a dichotomy has been established between "acute Q fever" and "chronic Q fever."[1] The term chronic Q fever was used due to the inability to determine the infected site in patients with persistent symptoms or a positive serology with an increase in phase I IgG, suggesting

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[a] Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, Faculté de Médecine, CNRS UMR 7278, IRD 198, Aix-Marseille Université, 27 Bd Jean Moulin, [b] Service de médecine nucléaire, Hôpital de La Timone, Marseille, [c] Service de pathologies infectieuses et tropicales de l'hôpital de Nimes, [d] Service de médecine, Hôpital de Chatellerault, [e] Unité Nord Insuffisance cardiaque et valvulopathies (UNIV), Service de cardiologie CHU de Marseille, Hôpital Nord, AP-HM Chemin des Bourrely, Marseille, [f] Service de Pathologies infectieuses et tropicales, CHU de Poitiers, [g] Service de Médecine interne Hôpital de Gap, [h] Service de Médecine interne, hôpital Saint Luc, Lyon, [i] Service de Rhumatologie, Centre hospitalier de Vienne, [j] Service de Pathologies infectieuses et tropicales, CHU de Rouen, [k] Service de Pathologies infectieuses et tropicales, CHU de Tours, [l] Service de Médecine Interne, CH de Bourges, [m] Service de Médecine Interne, Hôpital Saint-Anne, Toulon, [n] Service mobile d'Infectiologie, CH Victor Dupouy, Argenteuil, [o] Service de Médecine interne, CHU de Nantes, France.

[*] Correspondence: Didier Raoult, Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, Faculté de médecine, 27 boulevard Jean Moulin, 13005 Marseille, France (e-mail: didier.raoult@gmail.com).

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an active infection.[2] The term "chronic Q fever" is, however, misleading because it combines many different clinical entities under serological criteria.[3] Serological cut-offs alone are not sufficient to determine the persistence of *C burnetii* infection. This phenomenon is illustrated by the Q fever epidemic in French Guiana, where patients with primary Q fever presented high levels of phase I IgG with no systematic clinical progression towards a persistent focalized infection.[4] In France, *C burnetii* infection is endemic, but localized outbreaks and hyperendemic foci are described .[5] The disease is more often diagnosed in the Southeast of France where the French National Referral Center for Q fever is located.[5]

Endocarditis and vascular infections represent the majority of the described focalized persistent infections.[6,7] Several other localizations have been described, but less frequently, such as joint and bone infections,[8,9] lymphadenitis,[10] pericarditis, lung pseudo-tumor, and gall bladder infection.[11] In the case of endocarditis and vascular infections, definition scores have been elaborated, in which the ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) helps detecting infection focus (Table 1).[3] Thanks to an early diagnosis strategy, prophylaxis, and treatment, the prognosis of *C burnetii* endocarditis has drastically changed in our center.[6,12] The mortality rate has fallen from 60% to 5%.[6] However, vascular infections remain a very severe entity, with high mortality rates (up to 25%) and requiring surgical treatment.[7] In *C burnetii* joint and lymph node infections, very little is known about prognosis and treatment.[8–10] These differences in prognosis and treatment between the types of focalized Q fever infections illustrate the inaccuracy of grouping them under the global term of "chronic Q fever."

Nonetheless, in some circumstances, clinical symptoms and/or high IgGI antibodies persist without evident focus of infection. Physicians are confronted with therapeutic challenge, which is whether to treat a potentially fatal infection without knowing the site of infection or not. Moreover, classical morphological tools often fail to identify *C burnetii* infection because anatomical changes can be very slight. For example, in *C burnetii* persistent endocarditis, typical vegetation is observed in only 30% of cases, and echocardiography detected a valvular insufficiency in 75% of cases.[6] Vascular infections can be revealed only by aneurysm or vascular graft rupture.[13]

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography is an imaging modality that allows measurement of metabolic activity within an organ, obtained from the emission of positrons after disintegration of the injected radioactive product. As the majority of the malignant cells have high glycolytic activity, detection of their hypermetabolism was first used in clinical oncology.[14] Recently, it has been used for the identification of inflammatory and infectious processes because they also result in significant FDG uptake by the inflammatory cells. ^{18}F-FDG PET/CT has been used for the detection and monitoring of fever of unknown origin (FUO) and in a growing number of infections.[15,16] Regarding *C burnetii*, around 10 references are found in the literature reporting the use of ^{18}F-FDG PET/CT. Among these references, Barten et al reported 15 patients with *C burnetii* endocarditis and vascular infections.[17] Other reports describe hepatic, bone marrow, lymphadenitis, articular, and prostatic uptake of ^{18}F-FDG PET/CT.[8,17–23]^{18}F-FDG PET/CT has been included as a criterion in the definition scores for *C burnetii* endocarditis, articular prosthesis, and vascular infections. However, this definition was based on a very limited number of patients, and its utility in detection of other foci of infection has not been assessed.

Herein, our objective was to describe the different foci that could be detected in patients with persistent *C burnetii* infection. Thanks to this description, our secondary objective was to assess if ^{18}F-FDG PET/CT allowed the detection of a focus of infection in patients with unlocalized persistent *C burnetii* infection.

2. Patients and methods

2.1. Case definition

The French National Reference Center for Q fever receives samples for *C burnetii* testing[4] from the entire country. Between January 2009 and June 2015, 1555 patients were tested positive for Q fever in our center. Clinical and laboratory data were collected prospectively for all patients—thanks to a standardized questionnaire. For patients who did not benefit from a medical monitoring by our center in our center, data were collected over the phone to complete the standardized questionnaire.

All patients with an active *C burnetii* infection who benefited from a ^{18}F-FDG PET/CT were included in our study (Fig. 1 and eFig. 1, http://links.lww.com/MD/B217). Among these patients, several subgroups were identified and differentiated according to the diagnosis before ^{18}F-FDG PET/CT: primary *C burnetii* infection was defined by the association of clinical symptoms (fever and/or hepatitis and/or pneumonia) with serologic criteria for phase II IgG levels ≥200 and phase II IgM levels ≥50, or by a Polymerase Chain Reaction (PCR) and no endocarditis. Possible or definite *C burnetii* endocarditis, vascular infection, and joint prosthesis infection were defined according to the recent criteria (Table 1).[3,8] The rest of the cases were patients with persistent elevated phase I IgG (≥800) for more than 3 months without any focus of infection at clinical examination and transthoracic echocardiography.

We excluded patients for whom ^{18}F-FDG PET/CT was performed before the onset of symptoms that motivated the serology. Patients with serology indicative of a past resolved *C burnetii* infection were also excluded, and ^{18}F-FDG PET/CT examinations that were performed for follow-up were excluded (Fig. 1).

The study was approved by the local ethics committee (Comité de Protection des Personnes Sud Mediterranée 1). All patients gave informed consent.

2.2. Diagnosis of Coxiella burnetii infection

We used an indirect immunofluorescence assay to quantify IgG, IgM, and IgA titers against phase I and phase II, as previously described .[24] DNA was extracted using the QIAamp Tissue Kit (QIAGEN GmbH, Hilden, Germany), and these extracts were used as templates for PCR amplification as previously described.[25] Culture, immunohistochemistry, and fluorescent in situ hybridization (FISH) targeting *C burnetii* 16S rRNA were performed.[10,25]

2.3. ^{18}F-FDG PET/CT

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography was performed in the fasting state for at least 6 hours and the glucose level was lower than 150 mg/dL. An FDG dose of 4 to 5 MBq/kg was administered intravenously and imaging was performed 60 minutes after injection in accordance with each center's protocol. The images were analyzed visually

Table 1

Definition criteria for *C burnetii* endocarditis, vascular infections, and prosthetic joint arthritis.

Definition of Q fever endocarditis according to Raoult, 2012[3]	Definition of Q fever vascular infection according to Raoult, 2012[3]	Definition of *C burnetii*-related prosthetic joint arthritis according to Million, 2014[8]
Definite criterion:	Definite criterion:	Definite criterion:
Positive culture, PCR, or immunochemistry of a cardiac valve	Positive culture, PCR, or immunochemistry of an arterial samples (prosthesis or aneurism) or a periarterial abscess or a spondylodiscitis linked to aorta	Positive culture, polymerase chain reaction, or immunochemistry of a periprosthetic biopsy or joint aspirate
Major criteria	Major criteria	Major criteria
Microbiology: positive culture or PCR of the blood, an emboli or serology with IgG1 antibody titer ≥6400	Microbiology: positive culture, PCR of the blood or emboli, or serology with IgGI antibodies ≥6400	Microbiology
Evidence of endocardial involvement	Evidence of vascular involvement:	Positive culture or polymerase chain reaction of the blood
Echocardiogram positive for IE: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets or on implanted material in the absence of an alternative anatomic explanation; or abscess; or new partial dehiscence of a prosthetic valve; or new valvular regurgitation (worsening or changing of pre-existing murmur is not sufficient)	CT scan: aneurism or vascular prosthesis + periarterial abscess, fistula, or spondylodiscitis	Positive *C burnetii* serology with IgGI antibodies ≥6400
PET scan displaying a specific valve fixation and mycotic aneurism	PET scan specific fixation on an aneurism or vascular prosthesis	Evidence of prosthetic involvement:
		Computed tomography scan or MRI positive for prosthetic infection: collection or pseudo-tumor of the prosthesis
		Positron emission tomography scan or indium leukocyte scan showing a specific prosthetic hypermetabolism consistent with infection†
Minor criteria	Minor criteria	Minor criteria
Predisposing heart condition (known or found on echography)	Serological IgGI ≥800 <6400	Presence of a joint prosthesis (indispensable criteria)
Fever, temperature >38°C	Fever, temperature ≥38°C	Fever, temperature >38°C
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm (observed during PET scan), intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions.	Emboli	Joint pain
Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor	Underlying vascular predisposition (aneurism or vascular prothesis)	Serologic evidence: positive *C burnetii* serology with IgGI antibodies ≥800 and <6400 mg/dL
Serological evidence: IgG1 antibody titers ≥800 <6400		
Diagnosis definite	Diagnosis definite	Diagnosis definite
1A criterion	A criterion	1A criterion
2B criteria	2B criteria	2B criteria
1B criterion and 3C criteria (including 1 microbiological characteristic and a cardiac predisposition)	1B criterion and 2C criteria (including 1 microbiological characteristic and a vascular predisposition)	1B criterion and 3C criteria (including 1 piece of microbiology evidence and presence of a joint prosthesis)
Possible diagnosis	Possible diagnosis	Possible diagnosis
1B criterion and 2C criteria (including 1 microbiological characteristic and a cardiac predisposition)	Vascular predisposition, serological evidence, and fever or emboli.	1B criterion, 2C criteria (including 1 piece of microbiology evidence and presence of a joint prosthesis)
3C criteria (including 1 microbiological characteristic and a cardiac predisposition)		3C criteria (including positive serology and presence of a joint prosthesis)

C burnetii = *Coxiella burnetii*, PCR = polymerase chain reaction, PET = positron emission tomography, MRI = magnetic resonance imaging.

and semiquantitatively by measuring the maximum standardized uptake value (SUV-max). Hypermetabolic ^{18}F-FDG activity was considered as a potential site of infection when it did not correspond to physiological uptake (myocardial, liver, bladder, ureter, kidney, and gastrointestinal foci). ^{18}F-FDG PET/CT was performed in several centers without a common interpretation.

When the ^{18}F-FDG PET/CT was performed in another center, the protocol for ^{18}F-FDG PET/CT, images, and interpretation were collected retrospectively. When images were not available, reports alone were collected.

2.4. Main outcome: change of diagnosis after 18-FDG PET/CT

We considered that the ^{18}F-FDG PET/CT results allowed the diagnosis to be changed when a previously unknown localization

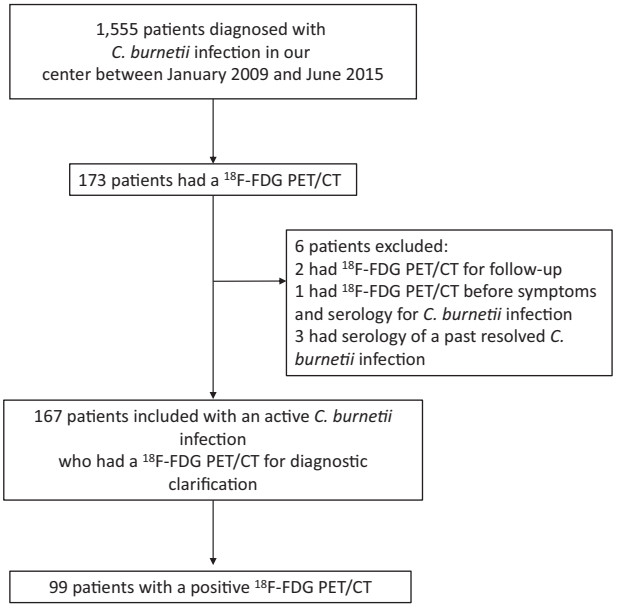

Figure 1. Flow chart.

of the infection was discovered, or when a possible endocarditis or vascular infection was confirmed.

2.5. Statistical analysis

Descriptive statistics for continuous variables are represented as median. Categorical variables are reported in terms of the number and percentages of patients affected. Variables were calculated using SPSS 22 Statistics Software.

3. Results

One hundred sixty-seven patients with *C burnetii* active infection had a ^{18}F-FDG PET/CT performed, including 37 women (22%) and 130 men (78%). The mean age of patients was 58.4 ± 16 years. The type of *C burnetii* active infection before ^{18}F-FDG PET/CT were: persistent elevated phase I IgG for more than 3 months for 57 patients (34%), possible endocarditis for 39 patients (23%), definite endocarditis or vascular infection for 31 patients (19%), primary Q fever for 25 patients (11.3%), possible vascular infection for 14 patients (8%), and possible osteoarticular infection for 1 patient (0.5%).

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography revealed positive hypermetabolism for 99 patients (59%). Fifty-seven of these patients (34.7% of all patients) had 1 hypermetabolism, 42 patients (15%) had 2 hypermetabolic foci, 10 (6%), and 3 patients (1.8%), respectively, had 3 and 4 hypermetabolic foci. The highest number of infectious foci located in 1 person was 5, which were found in 3 patients.

3.1. Osteoarticular localizations

Osteoarticular hypermetabolism was identified in 21 patients (Fig. 2 and Table 2). Osteoarticular localizations as the main focus of infection were observed in 8 cases (Fig. 2, Tables 2 and 3). Three infections involved a joint prosthesis. For 2 patients, we observed an acromioclavicular hypermetabolism, and 1 other patient had shoulder involvement (Figs. 2 and 3). One patient had tenosynovitis and another had an isolated spondylodiscitis.

Thirteen osteoarticular hypermetabolisms were associated with other hypermetabolic foci. In this context, we found a majority of spondylodiscitis (n = 9) complicating endocarditis or vascular infection (Table 3).

3.2. Lymphadenitis

Lymphadenitis hypermetabolism was identified in 27 patients (Figs. 2 and 3). Lymphadenitis was the sole focus for 11 patients, among which 7 (25%) also presented a primary *C burnetii* infection, and the remaining 4 were cases of isolated persistent lymphadenitis (14.8%). Lymphoma was diagnosed in 2 patients with lymphadenitis hypermetabolism.

Lymphadenitis hypermetabolism was associated with another persistent focalized infection in 16 cases (59%), with 5 patients presenting 3 or more concomitant foci. Cardiovascular foci were present in 5 cases (1 endocarditis, 4 vascular infections), osteoarticular foci in 6 cases (22%), and other foci are detailed in Table 2.

3.3. Endocarditis

A total of 21 patients (21%) showed a hypermetabolism suggesting endocarditis, including 6 hypermetabolisms on a native valve, 14 hypermetabolisms on a prosthetic valve, and 1 hypermetabolism on a pacemaker (Figs. 2 and 3). Before the ^{18}F-FDG PET/CT, these patients had possible endocarditis (n = 13), definite endocarditis (n = 3), persistent IgG1 (n = 3), suspicion of osteoarticular infection (n = 1), and suspicion of vascular infection (n = 1).

3.3.1. Endocarditis with aortic hypermetabolism and other embolic localizations. Eight patients with endocarditis had a simultaneous aortic hypermetabolism (6 Bentalls and 2 mycotic aneurysms) (Table 2). One of these patients had an associated spondylodiscitis and psoas abscess. One patient had a simultaneous spondylodiscitis and 3 had other articular foci.

3.4. Vascular infections

Twenty-six patients (26%) had a vascular hypermetabolism without endocarditis. Four of these patients had associated hyperfixating spondylodiscitis and psoas abscesses (Figs. 2 and 3). Diagnosis subgroups before^{18}F-FDG PET/CT were: possible vascular infections in 11 cases, definite vascular infections in 4 cases, possible endocarditis in 3 cases, definite endocarditis in 3 cases, persistent IgGI in 3 cases, and primary Q fever in 2 cases.

3.5. Bone marrow

Eleven patients presented an increased bone marrow uptake (Figs. 2 and 3). Among them, 4 presented a primary Q fever infection, 6 had a persistent cardiovascular focalized infection, 1 had an osteoarticular infection, 5 had a concomitant spleen hypermetabolism, and 4 had a concomitant lymphadenitis uptake. Four patients presented bone marrow uptake as the unique hypermetabolic focus (2 in a context of primary infection and 2 associated with nonhypermetabolic possible and definite endocarditis).

3.6. Pulmonary localization

For 9 patients, we observed a pulmonary hypermetabolism (Fig. 3). Five patients displayed conventional lobar pneumonia, and 2 had a hypermetabolic nodule. Four of them had a ^{18}F-FDG PET/CT in a context of primary Q fever (Table 2).

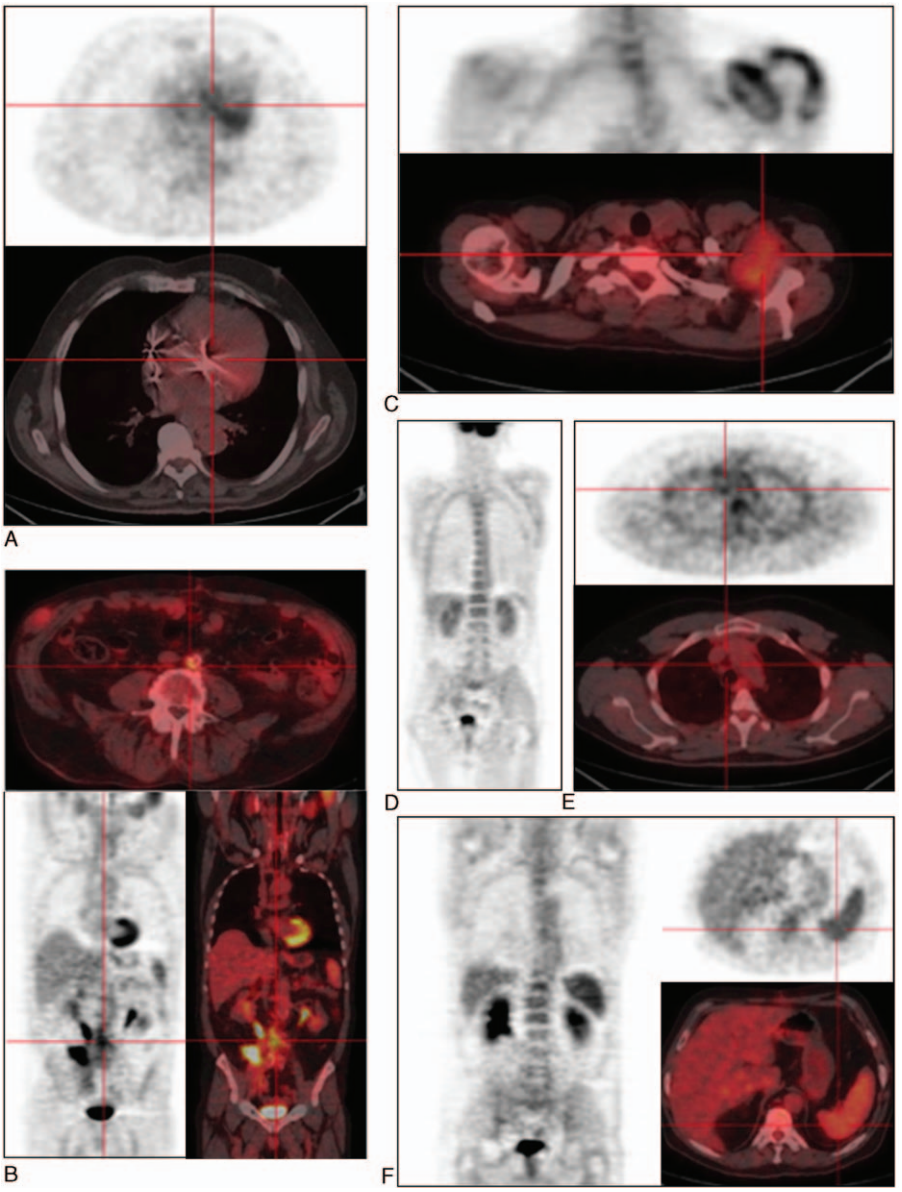

Figure 2. Hypermetabolic foci of *Coxiella burnetii* infection identified by ^{18}F-FDG PET/CT. A, Aortic valve hypermetabolism during definite Q fever endocarditis; B, abdominal aortic hypermetabolism during definite Q fever vascular infection; C, bursitis, arthritis foci during Q fever osteoarticualr infection; D, bone marrow hypermetabolism during Q fever; E, Q fever lymphadenitis identified with PET scan; F, spleen hypermetabolism during Q fever. ^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.

3.7. Other hypermetabolic foci

We observed the following other hypermetabolic foci: prostatic (5 patients), thyroid (4 patients), and laryngeal (4 patients). These foci were always associated with another main focus of infection.

3.8. Clinical relevance of ^{18}F-FDG PET/CT in the localization of Coxiella burnetii persistent focalized infection

Positive ^{18}F-FDG PET/CT allowed the diagnosis to be changed for 62 patients (62.6%). When the following 2 groups of patients were pooled, the first group being patients with isolated persistent elevated IgGI for more than 3 months and the second group being patients with possible endocarditis (n = 96), the diagnosis was changed in 55% of the patients—thanks to ^{18}F-FDG PET/CT. For patients with persistent isolated IgG1 (n = 57), the most frequent entities were an osteo-articular infection focus (n = 8, 30.7%) (Table 4) and lymphadenitis (n = 7, 26.9%) followed by endocarditis (n = 3), vascular infections (n = 3), lung pseudotumor (n = 2), and pulmonary hypermetabolism evocative of primary infection (n = 1; Figs. 2 and 3, Table 4). Six definite vascular infections were discovered in a context of suspicion of endocarditis (Table 4).

4. Discussion

We here report the largest case series of Q fever patients benefiting from a ^{18}F-FDG PET/CT. The mean age of patients (58 years) and the male predominance is concordant with the classic epidemiology of symptomatic Q fever.[26] More than half of these patients showed a positive ^{18}F-FDG PET/CT, and this examina-

Table 2

Description of 18F-FDG foci.

PET foci	Cardiac valve	Vascular	Osteoarticular	Lymphadenitis	Bone marrow	Pulmonar
N = positive ^{18}F-FDG PET/CT (% of total patients)	21 (12.5%)	34 (20.35%)	21 (12.5%)	27 (16%)	11 (6.5%)	9 (0.05%)
Age (mean)	63.6	65.8	64.95	60.83	52.7	57.81
Sex (M) (%)	17 (81%)	31 (91%)	19 (90%)	22 (81.5%)	9 (72%)	6 (66%)
IgG I (median)	2400	1200	600	800	200	800
IQR 25% percentile	800	700	400	400	100	25
IQR 75% percentile	12800	16000	1600	3200	800	2000
Associated hypermetabolism						
None	8	13	5	11	4	6
Endocarditis	ALL	8	2	1	0	0
Vascular infection	8	ALL	5	4	2	1
Osteoarticular	4	7	ALL	6	1	0
Bone marrow	0	3	1	4	ALL	1
Lymphadenitis	1	4	6	ALL	4	1
Spleen	2	4	1	4	5	1
Lung	0	1	0	1	1	ALL
Prostate	1	3	0	2	0	0

^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, IQR = interquartile range.

tion allowed the diagnosis to be changed in 62.6% of cases. Regarding hypermetabolism, it is that a high proportion of patients (42%) present 2 or more foci of fixation, reflecting the systemic nature of the *C burnetii* infection.

Because no gold standard imaging technique exists in the detection of *C burnetii* foci of infection, no statistical comparison could be made to assess the sensitivity and specificity of ^{18}F-FDG PET/CT, and this represents 1 limitation of our study. Patients diagnosed in our center may be followed in other cities, so that no common interpretation of ^{18}F-FDG PET/CT results was performed. This is another limitation of our study.

For patients with persistent elevated IgGI levels, we observed a focus of infection in 38.7% of cases. One striking finding is that the majority of these patients had an osteoarticular focus of infection (33%). This is an important result since osteoarticular Q fever infections have been considered to be rare occurrences, representing about 2% of Q fever cases.[27] The most widely reported localizations in the literature were osteomyelitis[20,28]

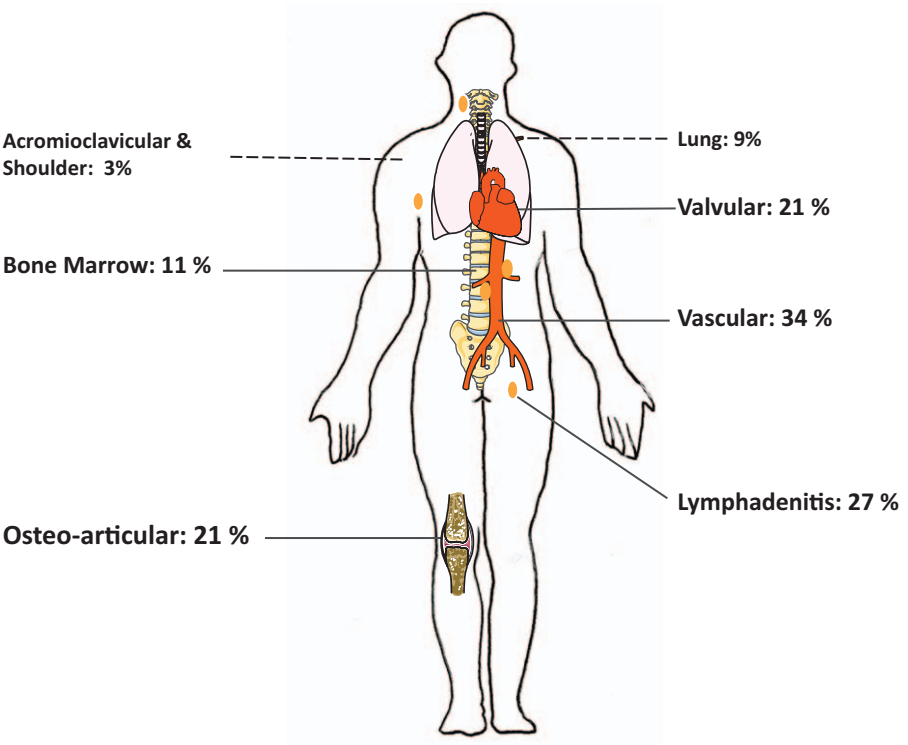

Figure 3. Distribution of Q fever foci identified by ^{18}F-FDG PET/CT. ^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.

Table 3

Details of the 8 patients with osteoarticular hypermetabolism as the main focus of infection.

Patient	Sex	Age	Indication for ^{18}F-FDG PET/CT	IgGI titer	Localization	Associated hypermetabolism
1	M	43	Isolated elevated IgGI	3200	Knee prosthesis	Bone marrow and lymph node
2	F	46	Isolated elevated IgGI	3200	Left shoulder	Contiguous lymph node
3	M	61	Isolated elevated IgGI	1600	Tibial tenosynovitis	None
4	M	56	Acute Q fever with bad evolution	3200	Acromio clavicular	Contiguous lymph node
5	M	68	Acute Q fever with bad evolution	25,600	Acromio clavicular	Contiguous lymph node
6	M	85	Isolated elevated IgGI	6400	Hip prosthesis	Contiguous lymph node
7	M	78	Isolated elevated IgGI	3200	Hip prosthesis	Mediastinal lymph node
8	M	80	Isolated elevated IgGI	800	Spondylodiscitis	No

^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.

and isolated spondylodiscitis.[29] Two cases of tenosynovitis of the wrist[29] and Q fever infections of a joint prosthesis have been reported.[8,30] We found only 1 case of isolated spondylodiscitis. All other cases of spondylodiscitis were associated with vascular infections or endocarditis. This result confirms that isolated *C burnetii* spondylodiscitis is quite rare. We observed 2 cases of acromioclavicular hypermetabolism with contiguous lymphadenopathy. Only 1 similar case of Q fever subacromial bursitis has been reported.[9] These 2 additional cases suggest a new Q fever clinical entity. We also reported here the fourth case of *C burnetii* tenosynovitis.[9,29] Thus, we suggest a new definition score for *C burnetii* osteoarticular infections (Table 5, part I). Definite criteria for diagnosis are microbiological proof (by PCR, culture, FISH, or immunohistochemistry) of infection in a bone or joint biopsy or joint fluid aspirate. Major and minor criteria are detailed in Table 5 (part I). Definite diagnosis of Q fever osteoarticular infection is defined by the presence of either 1 definite criterion, 2 major criteria, or 1 major and 3 minor criteria (Table 5, part I).

Q fever lymphadenitis was described in the literature as a proven microbiological focus of Q fever. *C burnetii* was identified within lymph nodes by PCR, immunohistochemistry, and FISH (eFig. 2, http://links.lww.com/MD/B217).[31] The use of ^{18}F-FDG PET/CT, however, has been anecdotally described in this setting. In a recent study, we described 59 cases of lymphadenitis associated with *C burnetii* infection, among which 42% were associated with persistent focalized infection.[31] Moreover, we recently demonstrated that *C burnetii* may predispose to lymphomagenesis.[31]^{18}F-FDG PET/CT is therefore a tool of choice for monitoring *C burnetii* lymphadenitis. Thus, we suggest a diagnostic score for *C burnetii* persistent lymphadenitis (Table 5, part II). *C burnetii* lymphadenitis is definite when the bacteria have been identified within lymph nodes by culture, PCR, immunohistochemistry, or FISH, or when 2 major criteria are fulfilled.

Bone marrow uptake was observed in both primary and persistent focalized infection and was associated in almost 50% of cases with spleen hypermetabolism, reflecting the lymphoid tropism of *C burnetii*. Bone marrow involvement during Q fever has been reported in cases of pancytopenia, hemophagocytic syndrome with aspects of doughnut granuloma,[18,32] and has also recently been described as a diffuse bone marrow ^{18}F-FDG PET/CT hypermetabolism.[19,33]

As mentioned in the literature, we found that ^{18}F-FDG PET/CT is particularly useful in the diagnosis of prosthetic valve endocarditis.[34] Of 21 patients with positive valvular ^{18}F-FDG PET/CT hypermetabolism, over two-thirds had a prosthetic cardiac valve. We described 1 case with pacemaker hypermetabolism. In over two-thirds of cases (71%), valvular hypermetabolism required us to change the diagnosis by confirming or revealing an endocarditis. This is particularly interesting in *C burnetii* endocarditis, where typical echocardiography findings such as vegetations are frequently lacking.[2] One-third of patients presented associated vascular or osteoarticular foci, supporting the usefulness of ^{18}F-FDG PET/CT in the detection of extracardiac complications of infective endocarditis.[35]

Thanks to ^{18}F-FDG PET/CT, we detected 34 vascular foci, 15 of them involving a vascular prosthesis (44%). In 6 cases, these

Table 4

Cases of change in diagnosis after 18F-FDG PET/CT.

	Diagnosis after 18F-FDG PET/CT							
Diagnosis before 18F-FDG PET/CT	Primary infection	Lymphadenitis	Definite endocarditis	Definite Vascular infection	Osteoarticular infection	Lung pseudotumor	Lymphoma	Total
Primary infection		3		2				5
IgGI ≥800 >3 mos	1	7	3	3	8	2		24
Possible endocarditis	1		13	3				17
Possible native vascular infection				11				11
Possible spondylodiscitis			1					1
Definite endocarditis				3				3
Definite native vascular infection							1	1
Total	2	10	17	22	8	2	1	62

^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.

Table 5

Definition criteria of *C burnetii* focalized infection.

(Part I) Definition of *C burnetii* osteoarticular infection (without prosthesis)	(Part II) Definition of *C burnetii* lymphadenitis
Definite criterion	Definite criterion
Positive culture, PCR or immunochemistry of bone or synovial biopsy, joint aspirate	Positive culture, PCR, immunohistochemistry, or fluorescence in situ hybridization of lymphadenitis
Major criteria	Major criteria
Microbiology:	Microbiology:
Positive culture or positive PCR of the blood	Positive culture or positive PCR of the blood
Positive serology with IgGI antibodies ≥800	Positive serology with IgGI antibodies ≥800
Evidence of bone or joint involvement:	Evidence of lymph node involvement:
Clinical arthritis, osteitis, or tenosynovitis	Clinical lymphadenitis
CT scan or ultrasonography (for joint) or MRI: osteo-articular destruction, joint effusion, intra-articular collection, spondylodiscitis, synovitis, acromio-clavicular localization	CT scan or ultrasonography (for joint) or MRI: lymphadenitis >1 cm
PET scan or indium leukocyte scan showing a specific osteo-articular uptake	PET scan showing a specific lymph node uptake
Minor criteria	Minor criteria
Serological IgGI ≥400 <800 mg/dL	Serological IgGI 400 <800 mg/dL
Fever, temperature ≥38°C	Fever, temperature ≥38°C
Mono or polyarthralgia	
Diagnosis definite	Diagnosis definite
1A criterion	1A criterion
2B criteria	2B criteria
1B criterion and 3C criteria (including 1 microbiological characteristic)	1B criterion and 2C criteria (including 1 microbiological characteristic)
Possible diagnosis	Possible diagnosis
1B criterion and 2C criteria	1B criterion and 1C criteria
3C criteria	2C criteria

I = definition of *C burnetii* osteoarticular infection (without prosthesis), II = definition of *C burnetii* lymphadenitis, *C burnetii* = *Coxiella burnetti*.

vascular foci involved a Bentall graft, so that these infections were systematically considered to be associated with prosthetic endocarditis, and 2 cases showed an associated hypermetabolism on a native valve. This shows that vascular *C burnetii* infections cover 2 different entities: primary infection of a pre-existing aneurysm or vascular graft (which seems to be the more frequent) and real "mycotic aneurysm" as a consequence of Q fever endocarditis. Historically, the definition of "mycotic aneurysm" was provided by Osler in 1885, with the description of a "mushroom-shaped" aneurysm secondary to infectious endocarditis embolism in the arterial wall.[36] These aneurysms are more frequently saccular. Thus, we think that the term "mycotic aneurysm" that has been used generically in several studies dealing with Q fever vascular infections[37] should be used only in the case of associated endocarditis, that is, in cases of valvulopathy associated with a vascular aneurysm in a context of Q fever infection. ^{18}F-FDG PET/CT, which provides a systemic view of infected foci, is a key tool in the distinction of these 2 clinical entities. Some hypermetabolic foci (prostatic, thyroid, and laryngeal) remain of unknown significance, so further studies are required to monitor these foci carefully to understand their meaning and specificity. Our study is 1 more argument for the use of 18-F-FDG PET/CT in the diagnosis of infectious diseases, as recommended by the European regulatory agency,[38] because it allows to change the diagnosis in *C burnetii* infection for 62% of cases upon discovering or confirming a focus of infection.

Because Q fever is a systemic infectious disease that can affect several organs at once, ^{18}F-FDG PET/CT imaging emerges as a revolutionary tool for localizing all foci of *C burnetii* infection. Moreover, our work is a new step in demonstrating that the notion of "chronic Q fever" is inadequate because it artificially combines significantly different persistent foci of infection. ^{18}F-FDG PET/CT helps achieve a more accurate identification of infected foci. For each of the foci described, we propose a sampling strategy to confirm the diagnosis of *C burnetii* infection, which can be made—thanks to several methods such as PCR, culture, immunohistochemistry, and FISH. All these new tools will encourage the development of specific prevention and treatment strategies for each type of *C burnetii* persistent focalized infection.

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