



FDG PET/CT for non-oncological indications

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BELGIAN SOCIETY OF NUCLEAR MEDICINE

Inspired by ...

Clinical and Translational Imaging
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EXPERT REVIEW



State of the art of ^{18}F -FDG PET/CT application in inflammation and infection: a guide for image acquisition and interpretation

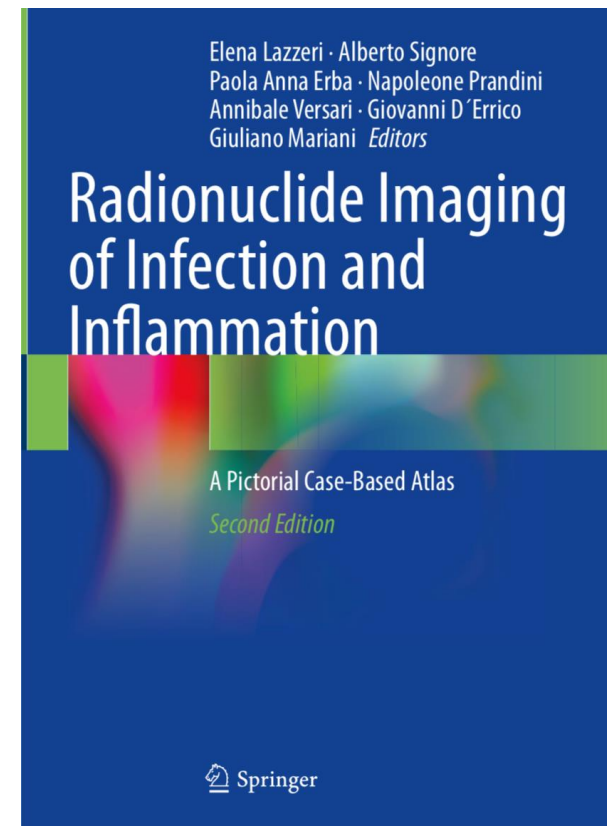
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EANM/SNMMI guideline/procedure standard for [^{18}F]FDG hybrid PET use in infection and inflammation in adults v2.0

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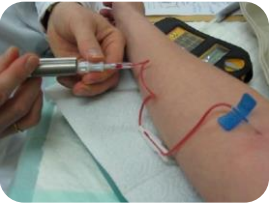
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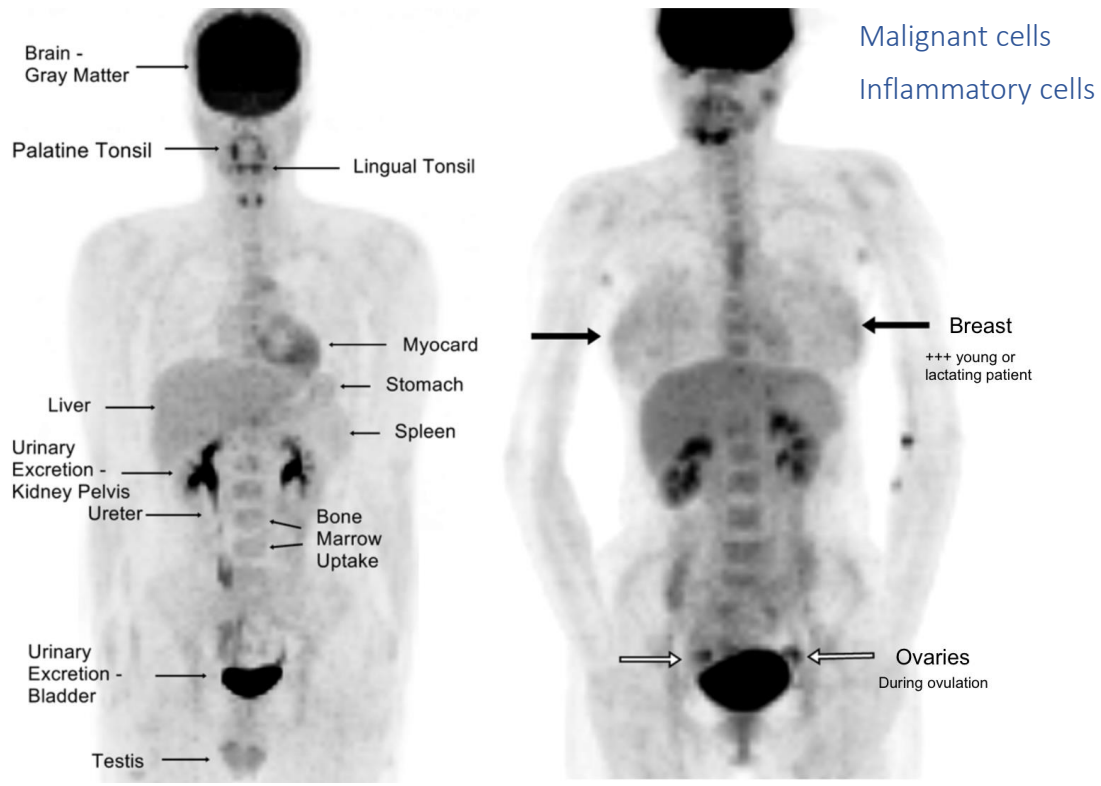
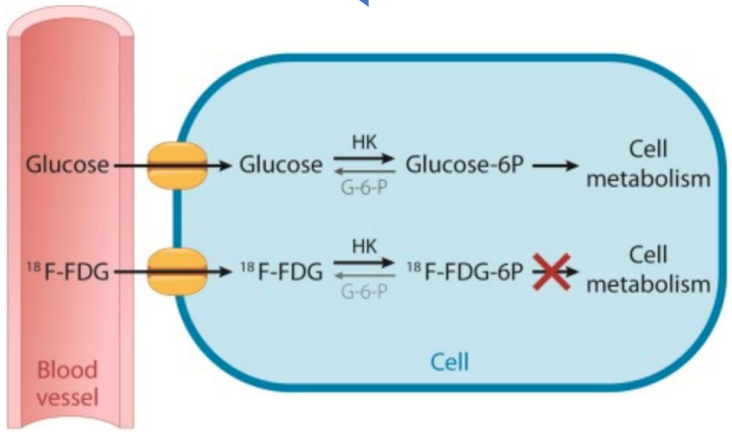


FDG PET/CT



^{18}F -FDG

Accumulates in cells with
✓ High glucose transport
✓ High glycolytic rates



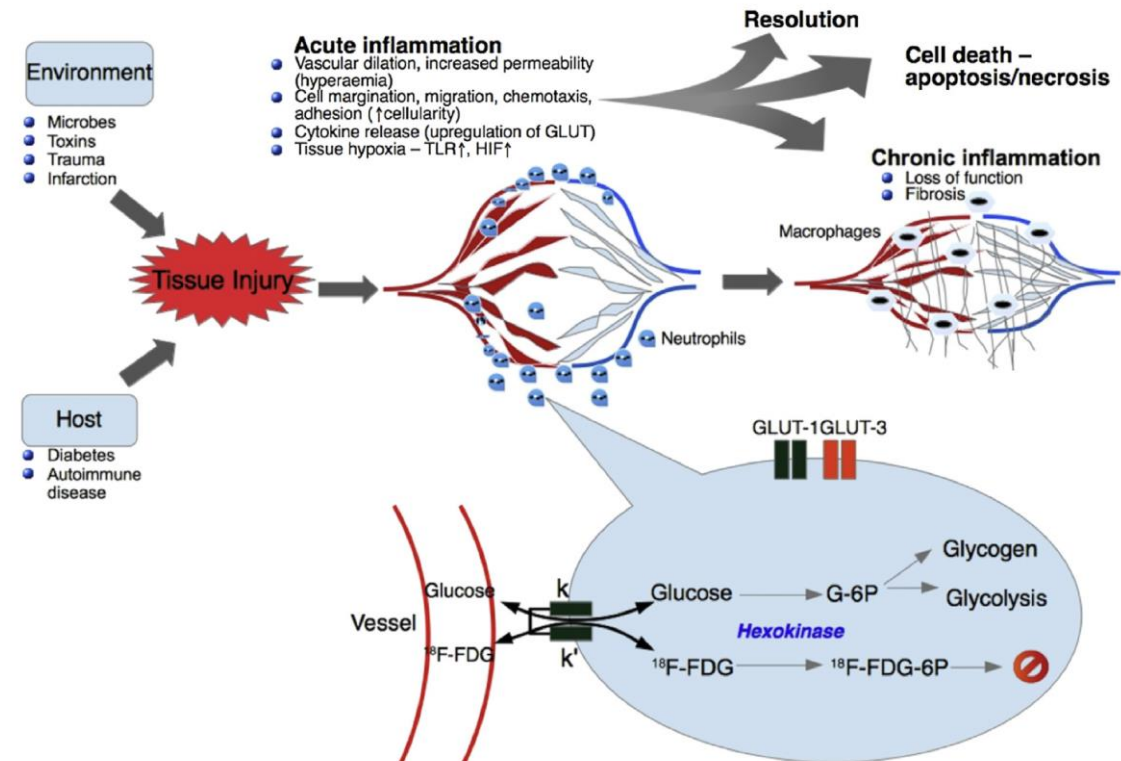
FDG PET/CT

Indications

- Oncology
- Neurology (neurodegenerative disorders, epilepsy)
- Inflammation/infection

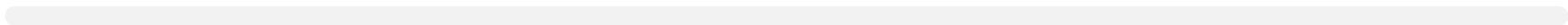
High sensitivity

Low specificity





Starting off with a first case

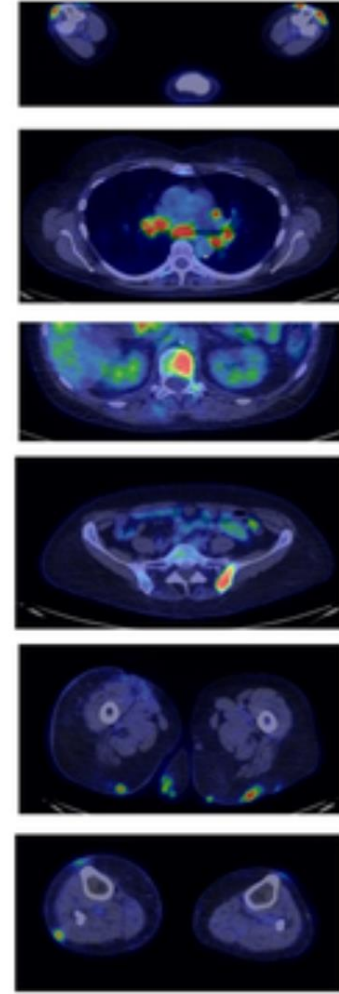




Metastatic melanoma



Ipilimumab and nivolumab



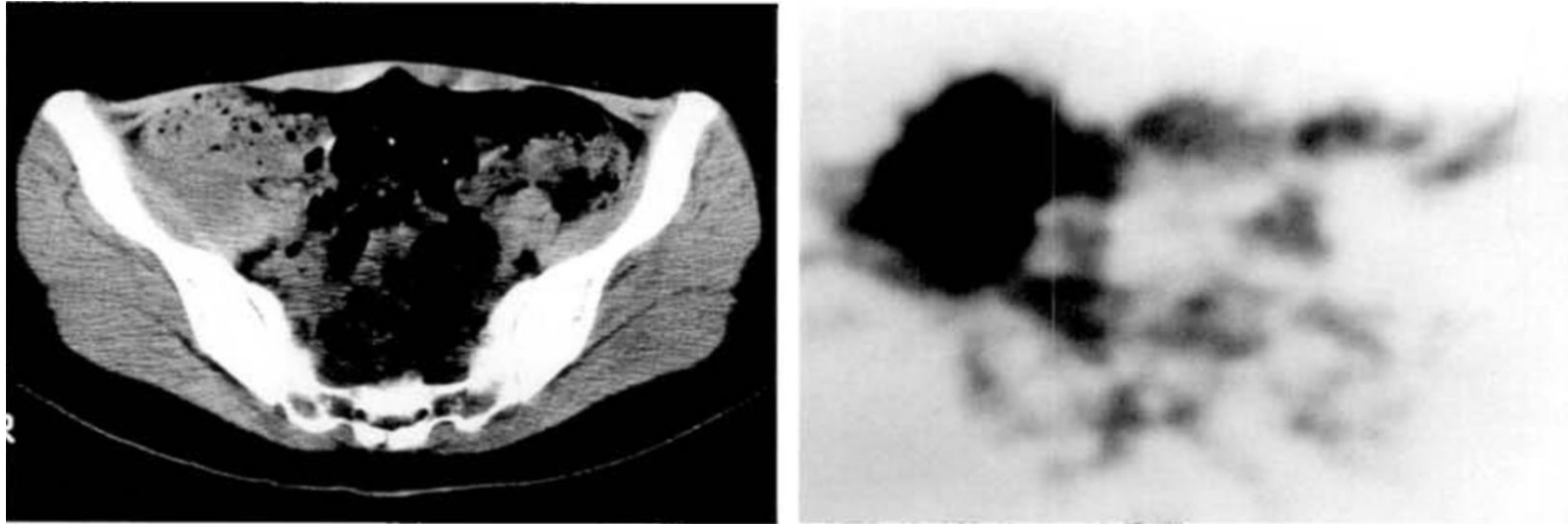
- ❑ Progression ?
- ❑ Complete metabolic response ?



Before the 2000's

Tahara T. Journal of Computer Assisted Tomography. 1989

21 year old woman with fever and lower abdominal pain



Paracolic abcess due to appendicitis



FDG PET/CT

High sensitivity

Not specific for infection

- Fever of unknown origin ←
- Bacteremia/sepsis ←
- Large vessels vasculitides
- Sarcoidosis ←
- Tuberculosis
- Endocarditis (PVE, NVE) ←
- LVAD and CIED infection ←
- Vascular prosthesis infection
- Spondylodiscitis
- AIDS (FUO, Lymphoma, TB, KS...)
- ...

White Blood Cell Scan

Specific for infection

Long delay injection-acquisition (0h-3h-24h)

Physiological bone marrow uptake

- Peripheral osteomyelitis
- Joint prosthesis infection
- Vascular prosthesis, LVAD and CIED infections
- Intra-abdominal infections (^{111}In)
- Pulmonary, CNS infections ...

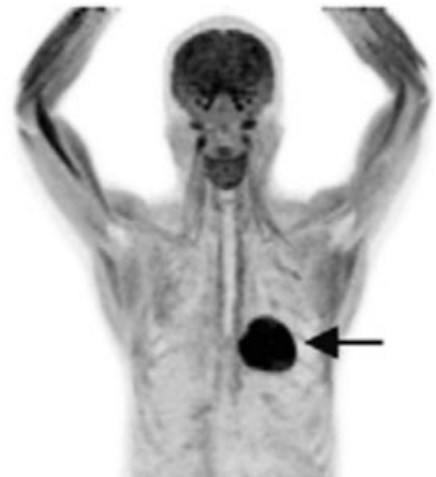
Bone Scintigraphy

- High NPV to rule out peripheral osteomyelitis
- Not specific : often needs to perform a complementary WBC scan.
- Not indicated to rule out PMR (→ FDG)

Fever of unknown origin (FUO) defined as **fever $\geq 38.3^{\circ}\text{C}$ persisting for at least 3 weeks, with no diagnosis despite 3 outpatient visits or in-patient days.**

CIED : cardiac implantable electronic devices (pacemakers, implantable cardiac defibrillators, and cardiac resynchronization therapy devices).

LVAD : Ventricular Assist Device.



1. ≥ 2 high-fat (>35 gm), low-carbohydrate (<3 gm) meals the day before PET



Breakfast

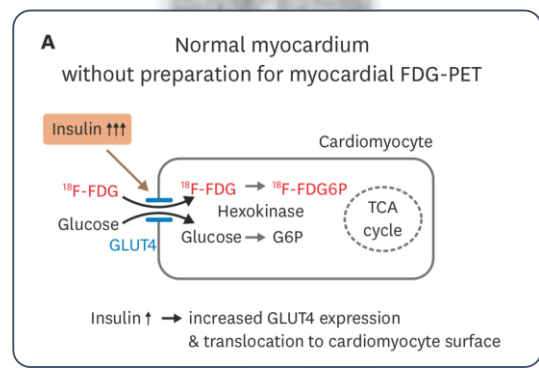


Lunch



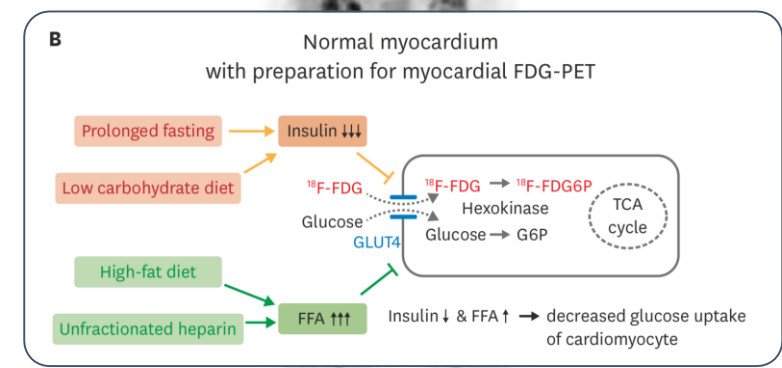
Dinner

2. Prolonged fasting
3. Heparin is optional (generally 50 IU/kg UFH 15 min before FDG inj)
4. No exercise for 24 hours before PET

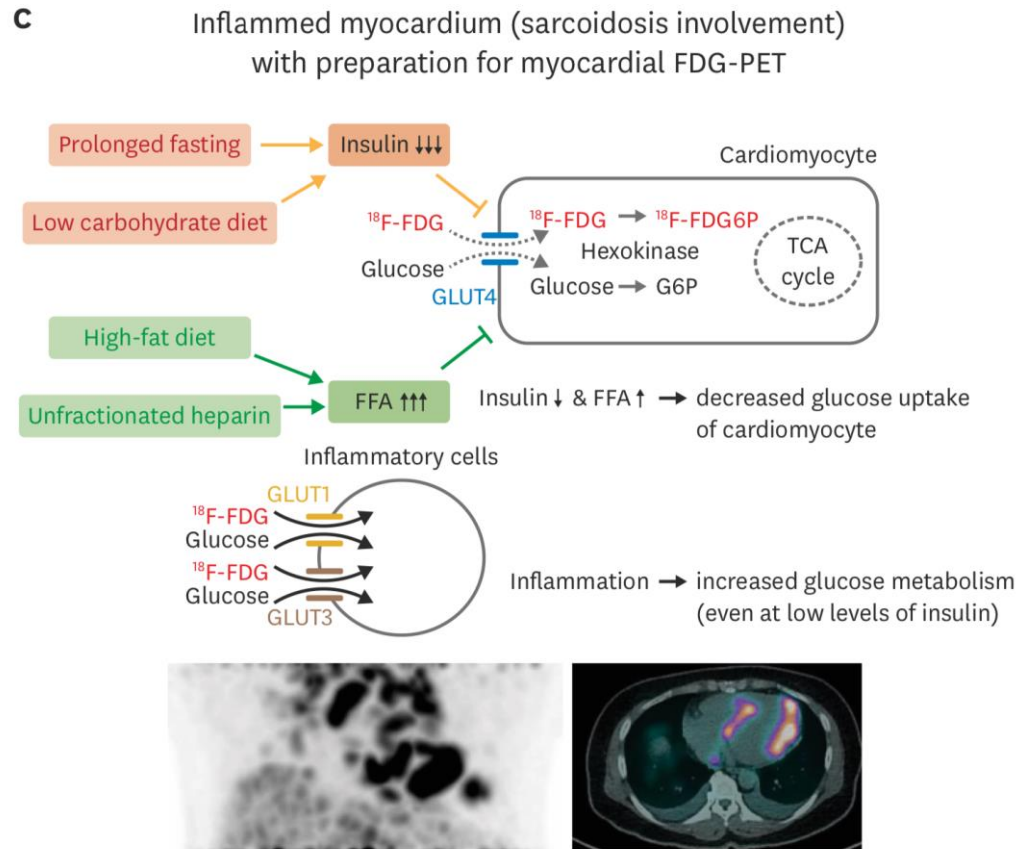


4-6h fasting

Hwang et al. J Cardiovasc Imaging. 2020



Myocardial suppression preparation

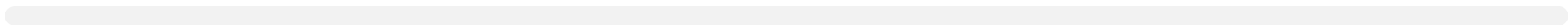


Indications a myocardial suppression preparation

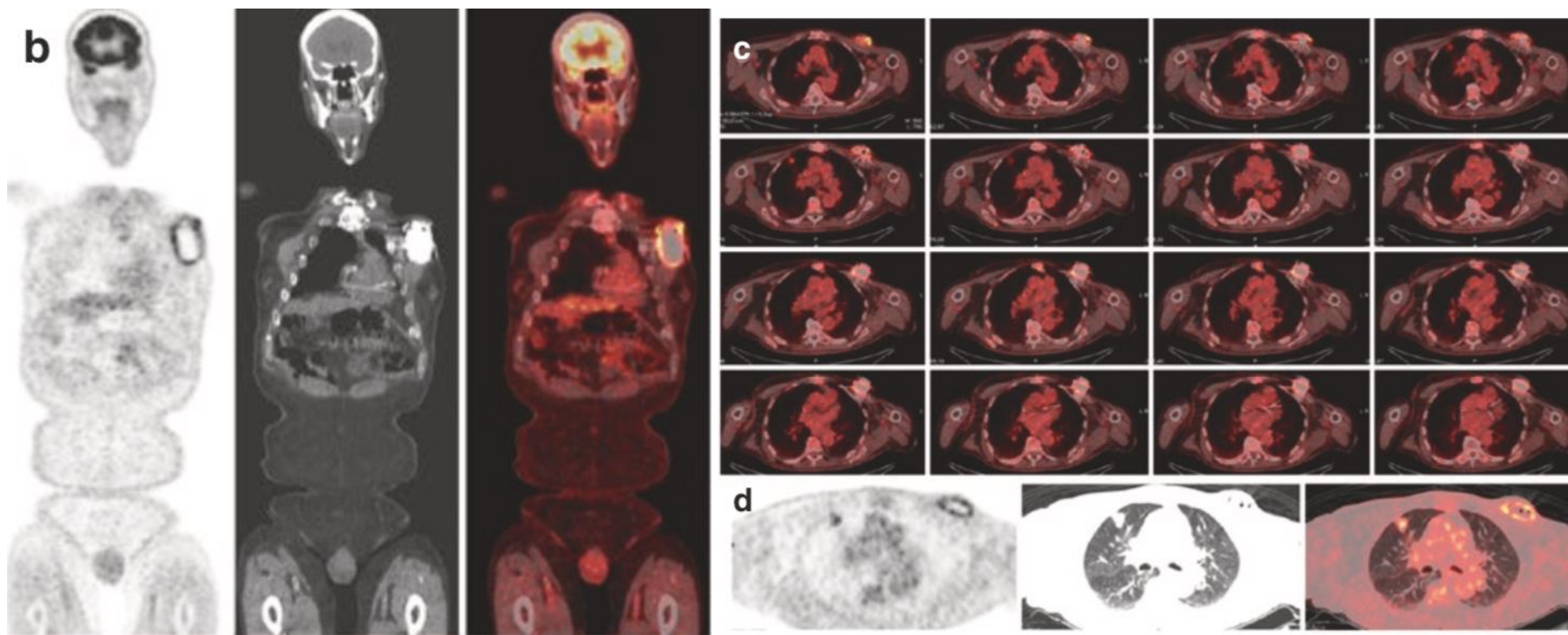
- Bacteremia/septicemia
- Endocarditis
- FUO with potential cardiac etiology
- Cardiac sarcoidosis
- CIED/LVAD infection



A case of bacteremia ...

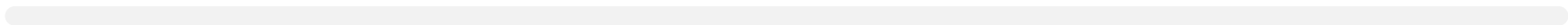


81 year-old man, pacemaker since 4 years. Fever. CRP et ESR ↑. Positive blood culture for *staphylococcus aureus*. Normal echocardiogram.



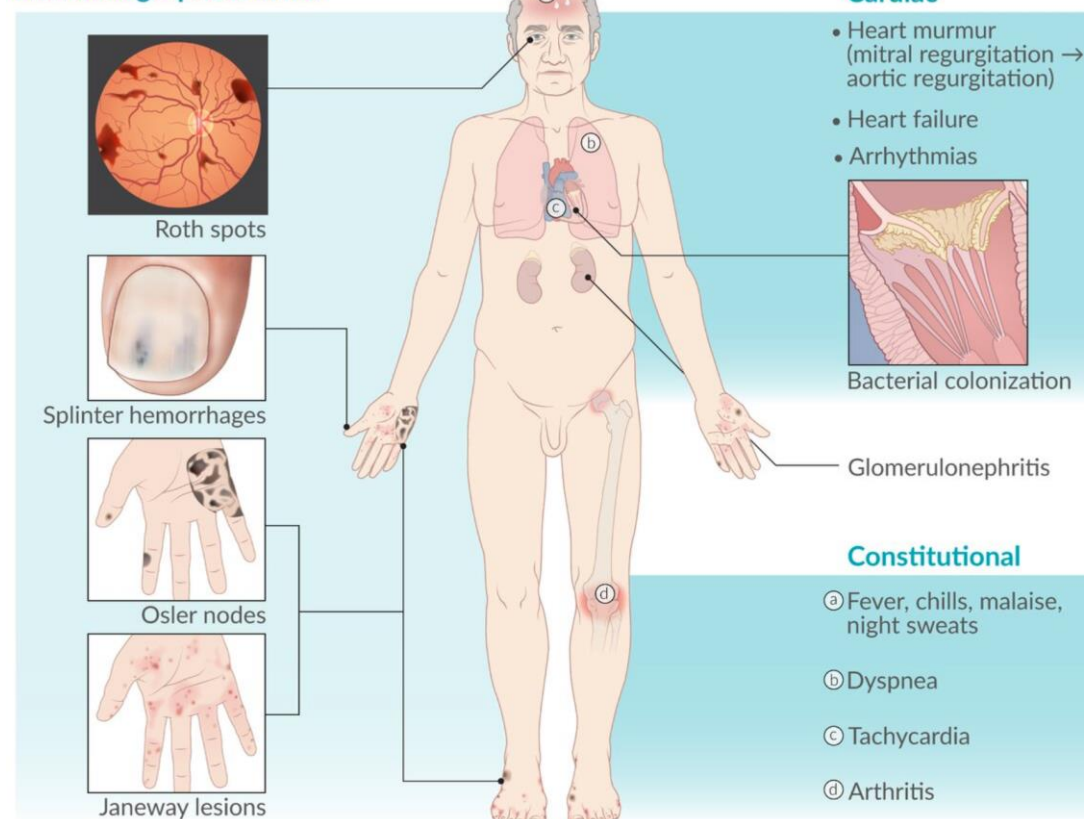


Infective endocarditis and CIED infections



Infective endocarditis

Peripheral embolic and immunologic phenomena



Micro-organisme (germe)	Fréquence (%)	Porte d'entrée
Staphylococcus aureus	30	Cutanée (plaies, cathéter veineux, cathéter de dialyse, toxicomanie IV, peropératoire, stimulateur/défibrillateur implantables, etc.)
Streptocoques oraux (S. sanguis, S. mitis, S. salivarius, S. mutans)	20	Buccodentaire
Streptocoques du groupe D (S. gallolyticus ou bovis)	13	Digestive (cancer, polypes, diverticules coliques)
Staphylocoques coagulase négative (S. epidermidis, S. lugdunensis, etc.)	10	Cutanée (plaies, cathéter veineux, cathéter de dialyse, toxicomanie IV, peropératoire, stimulateur/défibrillateur implantables, etc.)
Entérocoques (E. faecalis, E. faecium)	10	Digestive (cancer, polypes, diverticules coliques) Urinaires
Bactéries du groupe HACEK	5	Bucco-dentaire
Candida et autres champignons	< 5	Cutanée (immunosuppression, cathéter veineux, cathéter de dialyse, toxicomanie IV, peropératoire, stimulateur/défibrillateur implantables, etc.)
Autres (Coxiella burnetii, Bartonella, Brucella, Chlamydia, Tropheryma whippelii, etc.)	< 5	Spécifique à chaque germe

Risk factors of native valve endocarditis (NVE) : valvular abnormalities (e.g. bicuspid aortic valve), previous history of NVE and intravenous drug use ...

Prosthetic valve endocarditis (PVE) represents **20%** of all cases of infective endocarditis.

Infective endocarditis

Major criteria
(i) Blood cultures positive for IE (a) Typical microorganisms consistent with IE from two separate blood cultures: Oral streptococci, <i>Streptococcus gallolyticus</i> (formerly <i>S. bovis</i>), HACEK group, <i>S. aureus</i> , <i>E. faecalis</i> (b) Microorganisms consistent with IE from continuously positive blood cultures: • ≥ 2 positive blood cultures of blood samples drawn >12 h apart. • All of 3 or a majority of ≥ 4 separate cultures of blood (with first and last samples drawn ≥ 1 h apart). (c) Single positive blood culture for <i>C. burnetii</i> or phase I IgG antibody titre $>1:800$.
(ii) Imaging positive for IE: Valvular, perivalvular/periprosthetic and foreign material anatomic and metabolic lesions characteristic of IE detected by any of the following imaging techniques: • Echocardiography (TTE and TOE). • Cardiac CT. • [18F]-FDG-PET/CT(A). • WBC SPECT/CT.
Minor criteria
(i) Predisposing conditions (i.e. predisposing heart condition at high or intermediate risk of IE or PWIDs)^a (ii) Fever defined as temperature $>38^{\circ}\text{C}$ (iii) Embolic vascular dissemination (including those asymptomatic detected by imaging only): • Major systemic and pulmonary emboli/infarcts and abscesses. • Haematogenous osteoarticular septic complications (i.e. spondylodiscitis). • Mycotic aneurysms. • Intracranial ischaemic/haemorrhagic lesions. • Conjunctival haemorrhages. • Janeway's lesions.
(iv) Immunological phenomena: • Glomerulonephritis. • Osler nodes and Roth spots. • Rheumatoid factor.
(v) Microbiological evidence: • Positive blood culture but does not meet a major criterion as noted above. • Serological evidence of active infection with organism consistent with IE.

Limitations of echocardiography

- If negative, does not rule out the diagnosis.
- Can be negative at an early stage ($\rightarrow$ repeat after 7 days)
- Low sensitivity for in case of PVE (70% vs 96% for NVE)

Recommendation Table 5 — Recommendations for the role of echocardiography in infective endocarditis

Recommendations	Class ^a	Level ^b
A. Diagnosis		
TTE is recommended as the first-line imaging modality in suspected IE. ^{166,179}	I	B
TOE is recommended in all patients with clinical suspicion of IE and a negative or non-diagnostic TTE. ^{166,178,179}	I	B
TOE is recommended in patients with clinical suspicion of IE, when a prosthetic heart valve or an intracardiac device is present. ^{166,178,179}	I	B
Repeating TTE and/or TOE within 5–7 days is recommended in cases of initially negative or inconclusive examination when clinical suspicion of IE remains high. ¹⁷⁸	I	C
TOE is recommended in patients with suspected IE, even in cases with positive TTE, except in isolated right-sided native valve IE with good quality TTE examination and unequivocal echocardiographic findings. ^{165,166,179}	I	C
Performing an echocardiography should be considered in <i>S. aureus</i> , <i>E. faecalis</i> , and some <i>Streptococcus</i> spp. bacteraemia. ^{19,149,174}	IIa	B



Infective endocarditis

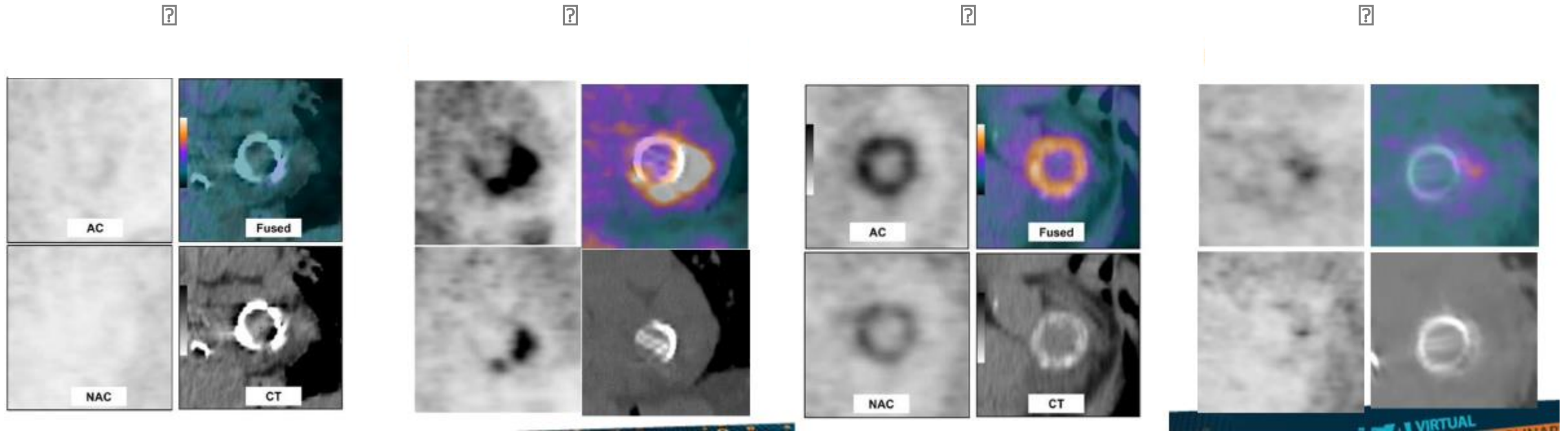


Image reorientation in the valve plane allows for better assessment of $[^{18}\text{F}]\text{FDG}$ distribution.

Infective endocarditis

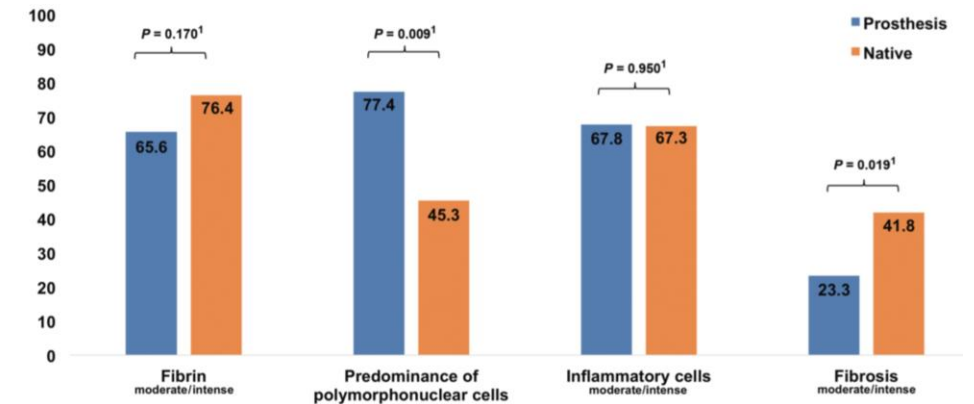
Table 8 Major performance values of meta-analyses for PVE with [¹⁸F]FDG PET/CT

Authors	No. studies (patients)	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood Ratio + (95% CI)	Likelihood Ratio - (95% CI)	DOR (95% CI)
Juneau et al. [65] (2018)	7 (NR)	85% (77-91)	81% (72-88)	NR	NR	NR
Mahmood et al. [66] (2019)	8 (NR)	81% (74-86)	73% (64-81)	NR	NR	NR
Wang et al. [67] (2020)	15 (634)	86% (81-89)	84% (79-88)	3.23 (1.75-5.95)	0.21 (0.14-0.32)	22 (10-48)

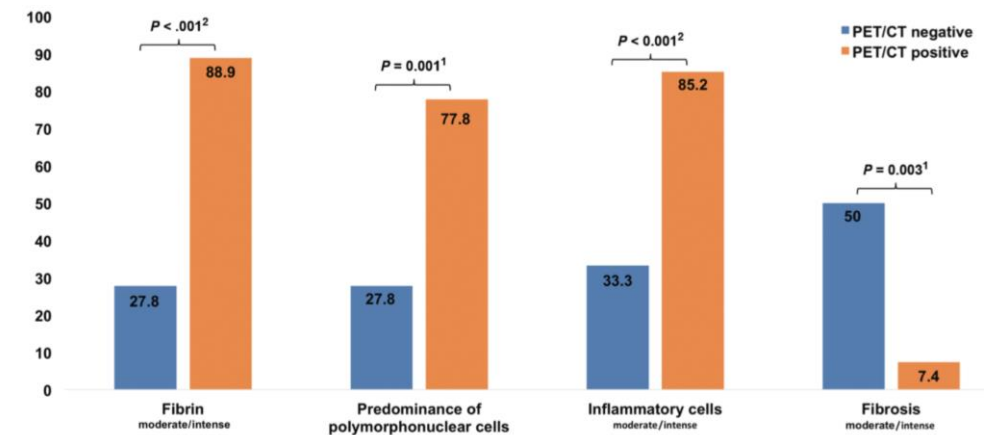
Table 9 Major performance values of meta-analyses for NVE with [¹⁸F]FDG PET/CT

Authors	No. studies (patients)	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood Ratio + (95% CI)	Likelihood Ratio - (95% CI)	DOR (95% CI)
Wang et al. [67] (2020)	4 (297)	31% (21-41)	98% (95-99)	14.0 (5.6-35.4)	0.71 (0.60-0.84)	23.0 (8.1-65.6)
Kamani et al. [77] (2020)	7 (351)	36% (22-54)	99% (89-100)	8.3 (3.7-18.3)	0.6 (0.27-1.33)	15.3 (6.1-38.4)

Surgically resected cardiac valves of 145 patients with infective endocarditis :

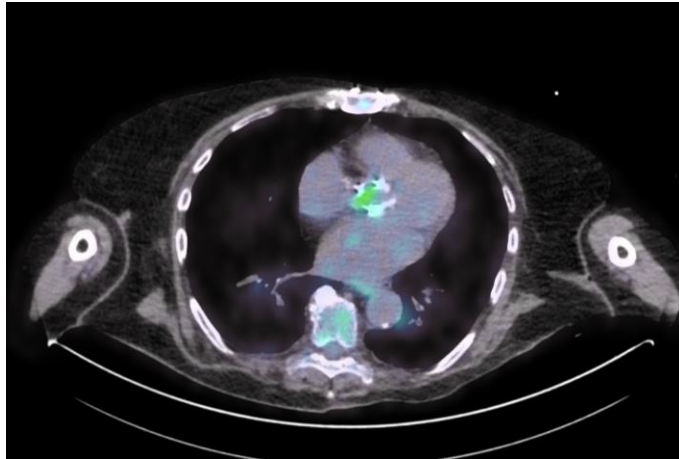


FDG-PET/CT uptake pattern of surgically resected cardiac valves of 45 patients with suspected infective endocarditis.

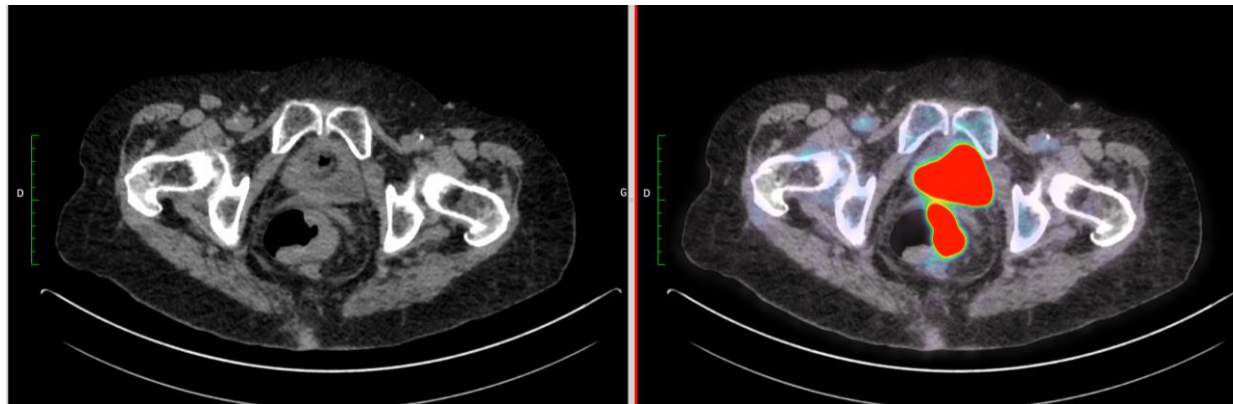




Infective endocarditis

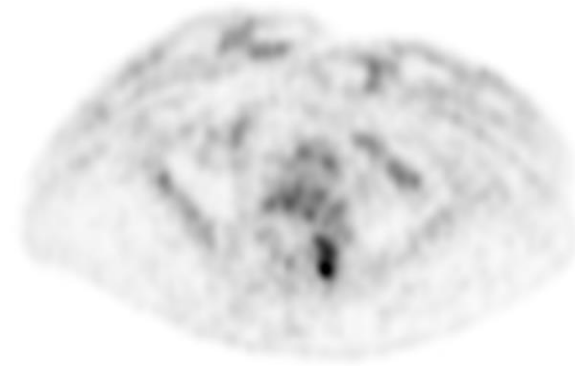
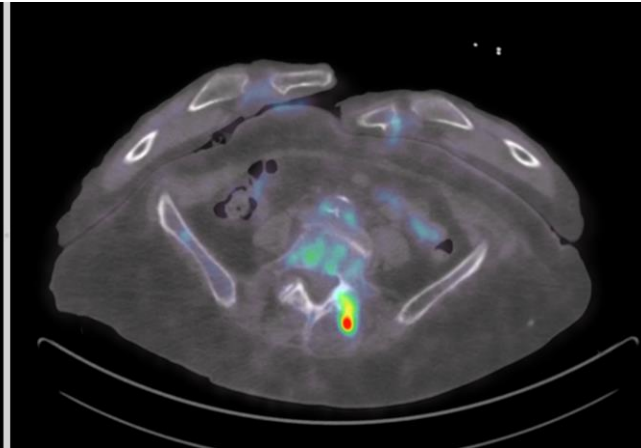
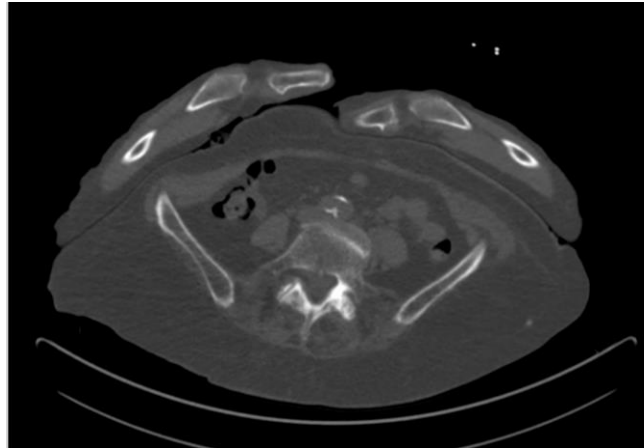
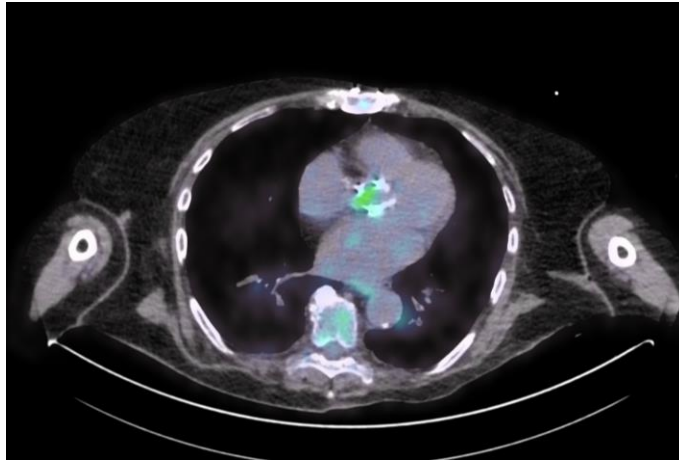


Acquisition FOV encompassing the vertex-to-toes is recommended to evaluate for **suspected emboli** and to **identify the source of bacteremia**.



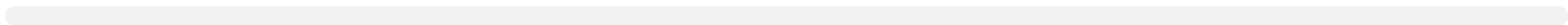


Infective endocarditis



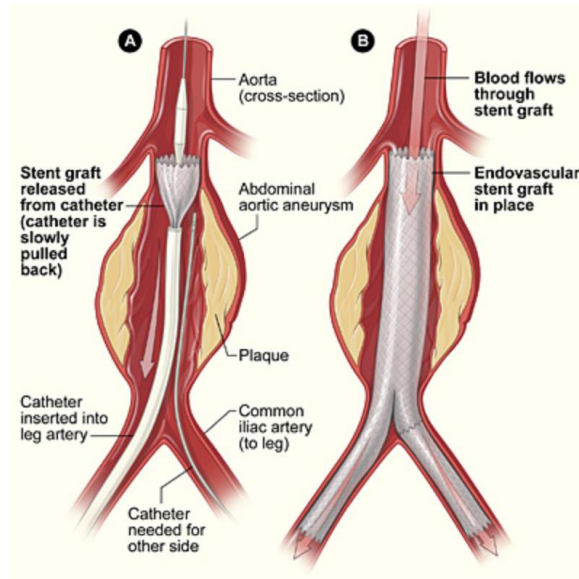


Vascular graft/endograft infections

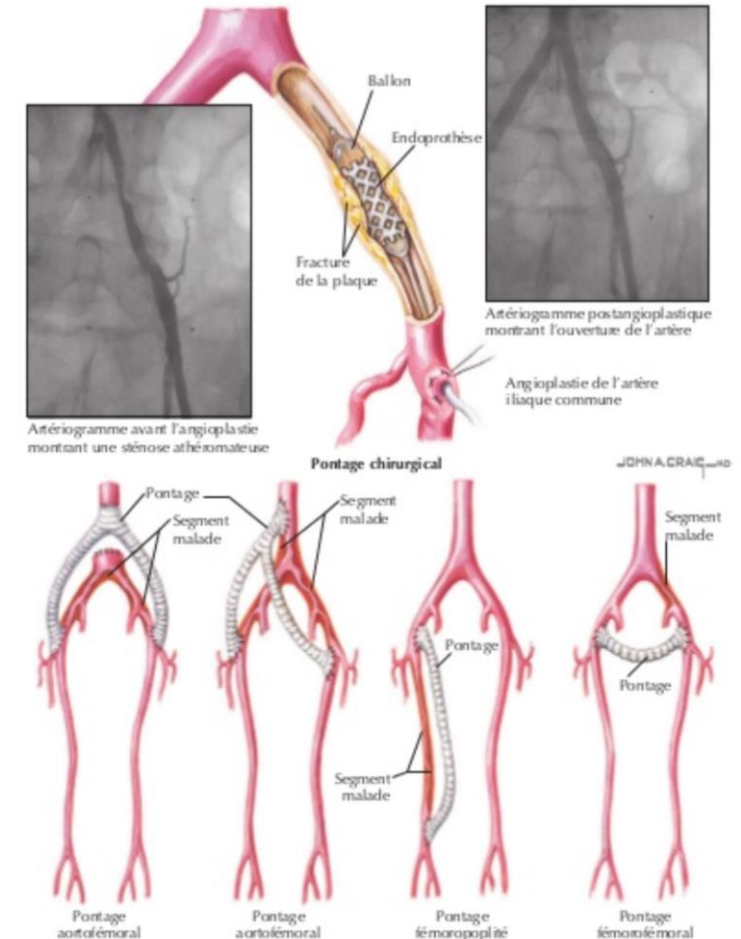


Vascular graft/endograft infection

- Vascular grafts :
 - Life-threatening aortic aneurysms and dissections
 - Occlusive peripheral artery disease

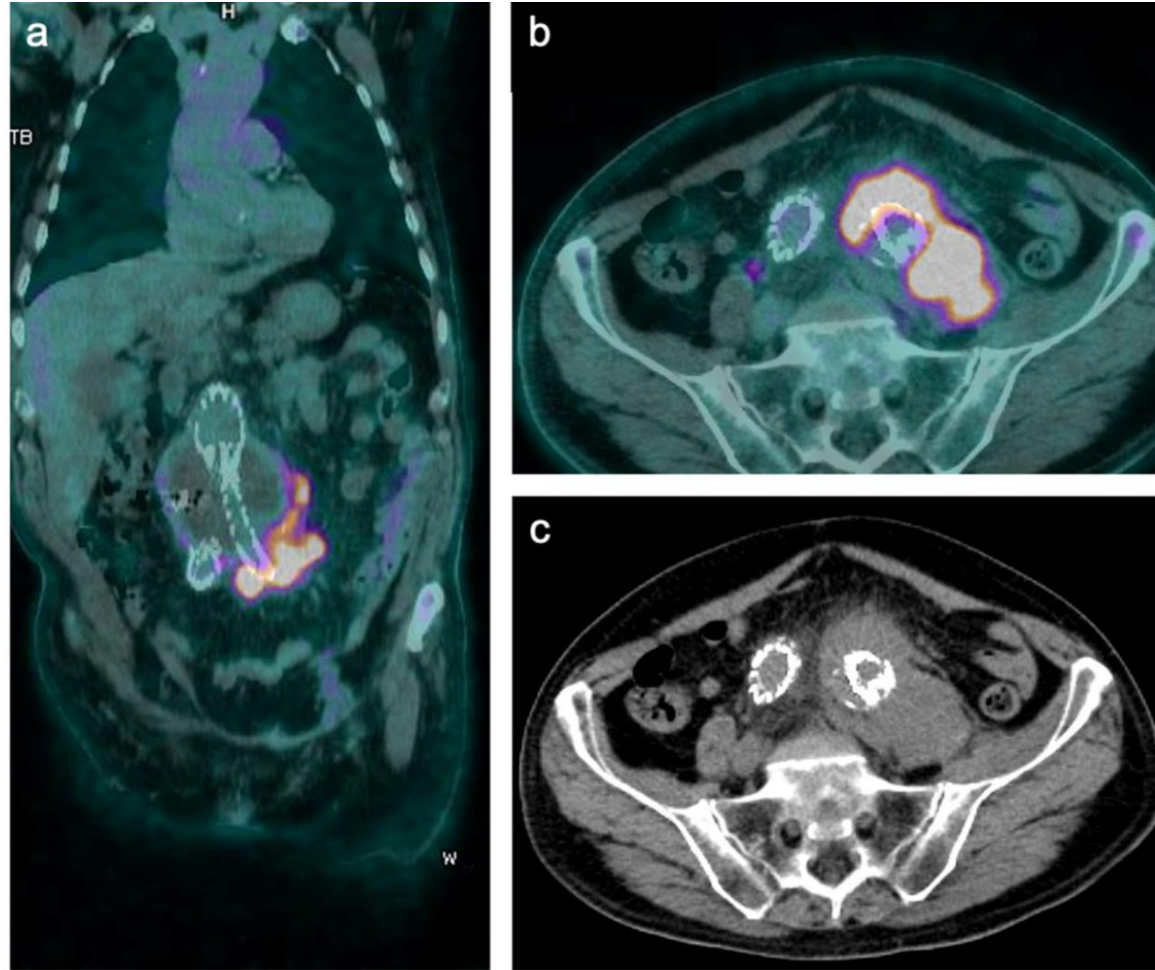


Endovascular aneurysm repair (EVAR)



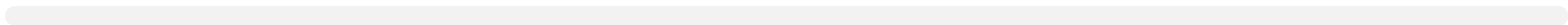


Vascular graft/endograft infection





Fever of unknown origin... in elderly patients







US Bayard Taylor Horton
1895-1980

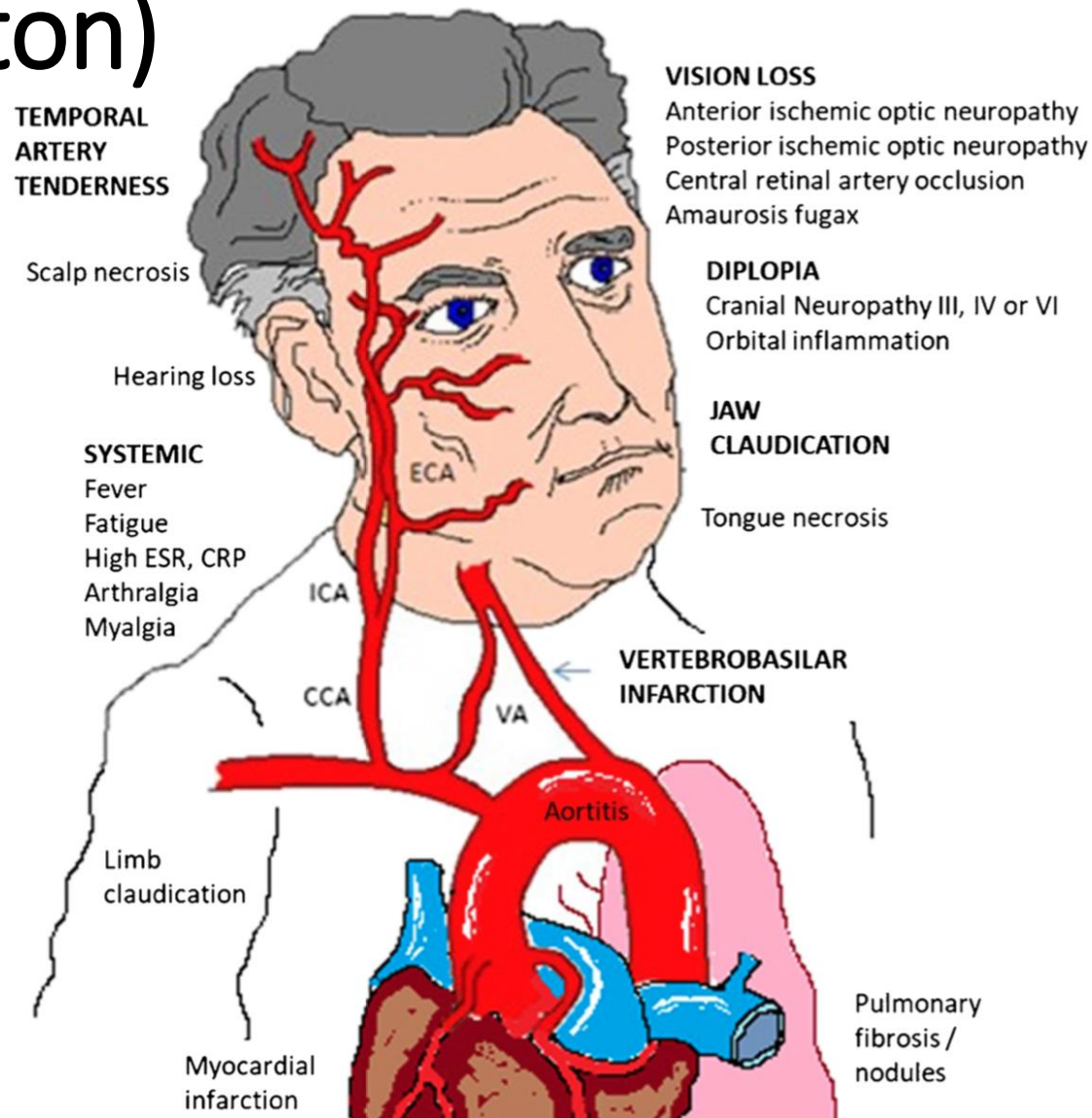
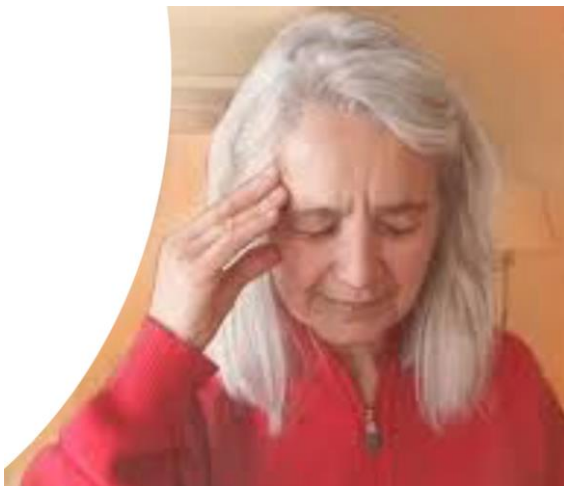
Large vessel vasculitis

Giant Cell Arteritis (Horton) and Takayasu's arteritis



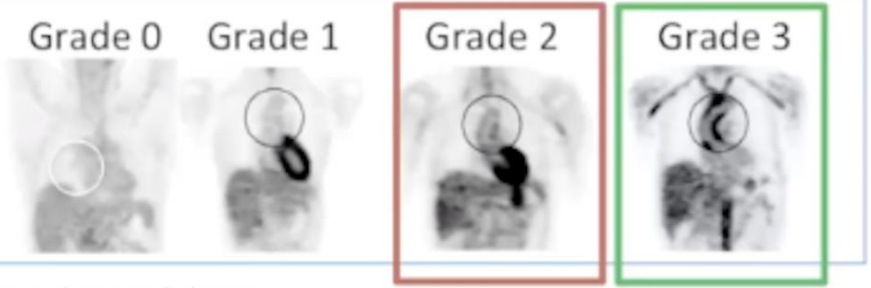
JP 高安 右人
1860-1938

Giant Cell Arteritis (Horton)

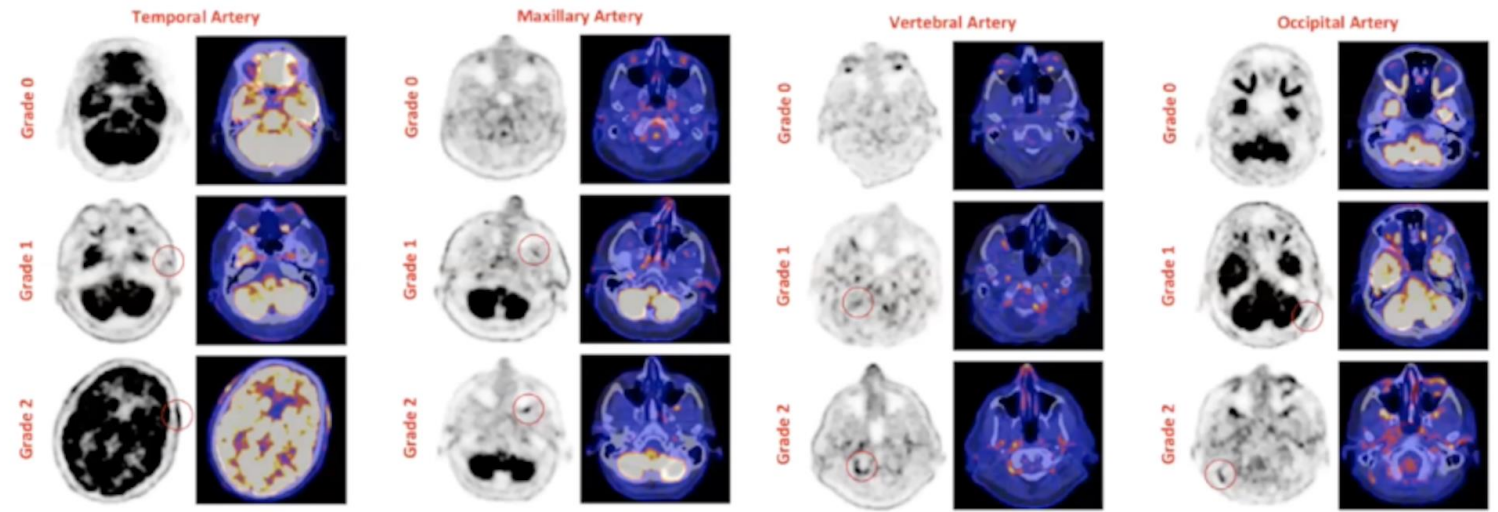




Grade 0 = no uptake
Grade 1 = minimal uptake (< liver)
Grade 2 = moderate uptake (= liver)
Grade 3 = marked uptake (> liver)



Increased acquisition time of **cranial** FOV and high-resolution reconstruction are recommended for assessment of cranial arteries.



- Grade 0 : no uptake above surrounding tissue
- Grade 1 : uptake just above surrounding tissue
- Grade 2 : uptake significantly above surrounding tissue





What if the patient is has been already on methylprednisolone (medrol®) since two weeks ? ❓

Clinical Trial > [Eur J Nucl Med Mol Imaging](#). 2018 Jul;45(7):1119-1128.

doi: 10.1007/s00259-018-4021-4. Epub 2018 Apr 18.

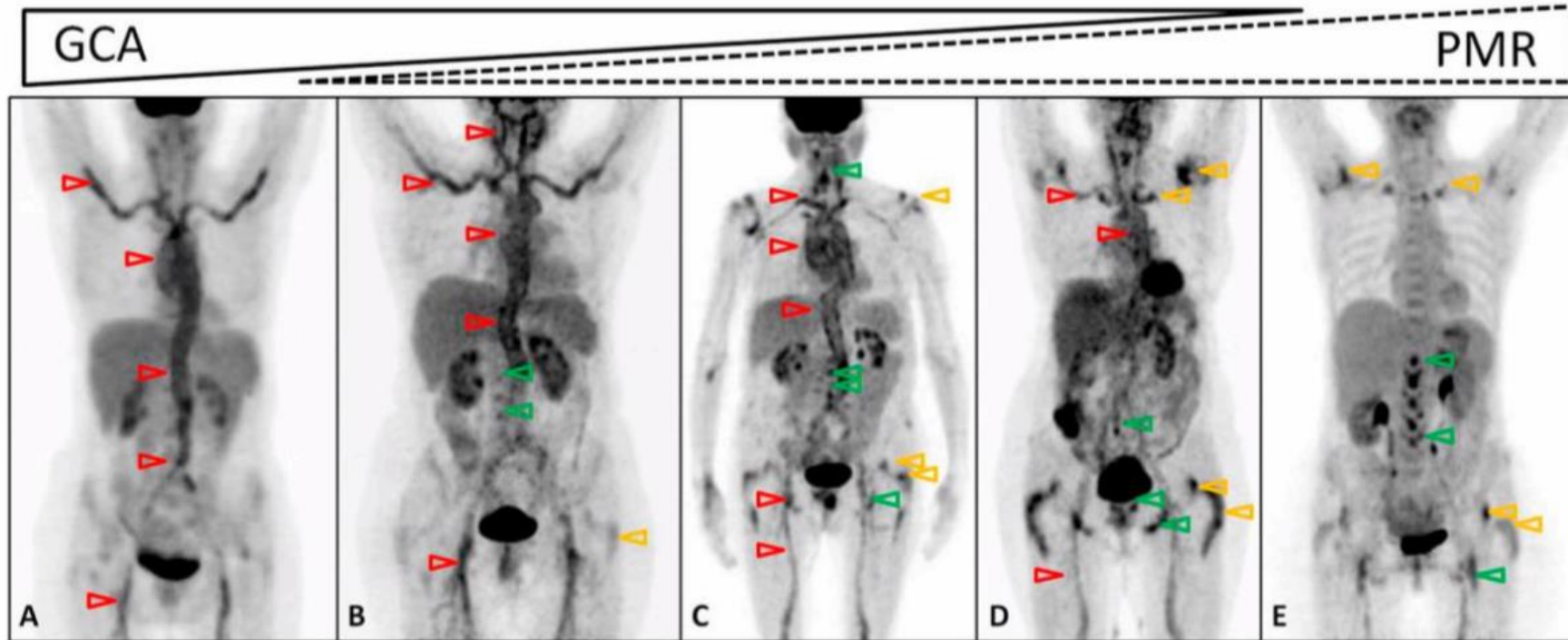
Three days of high-dose glucocorticoid treatment attenuates large-vessel 18F-FDG uptake in large-vessel giant cell arteritis but with a limited impact on diagnostic accuracy

Oral

Conclusions: Within 3 days of high-dose glucocorticoid treatment, FDG PET/CT can diagnose LV-GCA with high sensitivity. This window of opportunity ensures that prompt glucocorticoid treatment can be initiated to avoid debilitating GCA complications with a limited effect on diagnostic accuracy. After 10 days of treatment, FDG PET/CT sensitivity decreases significantly.

What about Polymyalgia Rheumatica (PMR) ?

FR *Pseudopolyarthrite rhizomélisque (PPR)*



Rehak Z et al. Br J Radiol. 2017

Acquisition should encompass a **vertex-to-knees** FOV and should be performed with arms next to the body.



What about Polymyalgia Rheumatica (PMR) ?

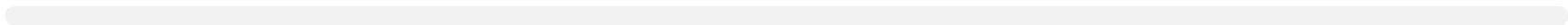
Bone scintigraphy ?

LOW SPECIFICITY and LOW SENSITIVITY





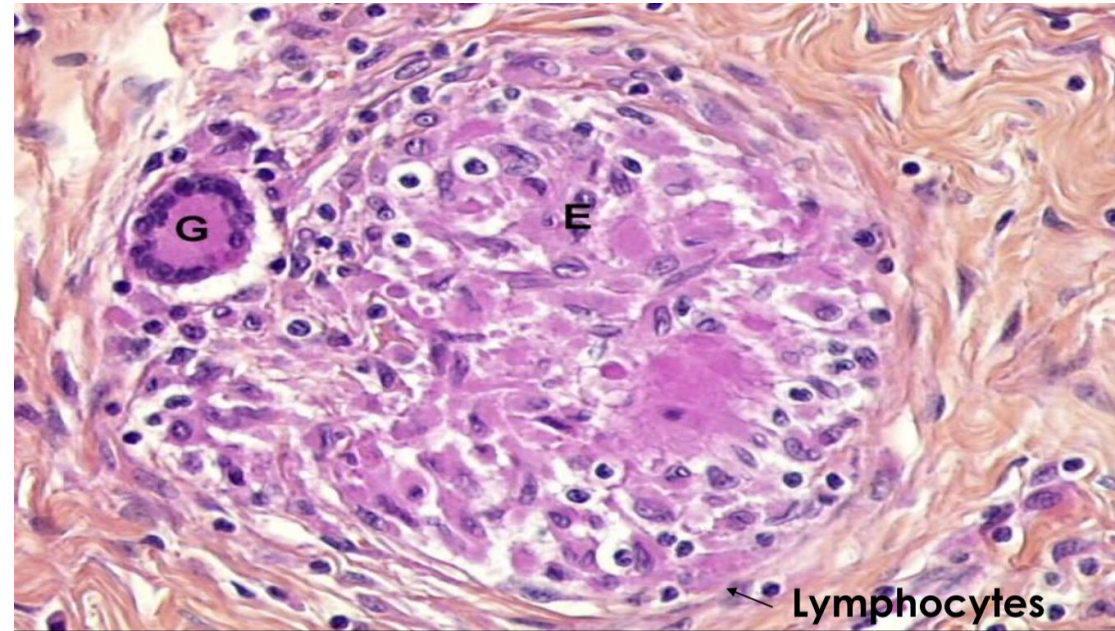
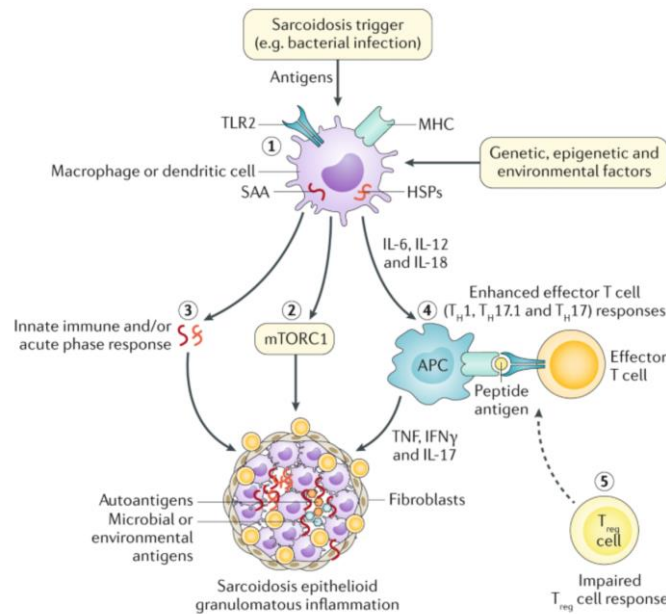
Sarcoidosis





σάρξ σαρκός

Sarcoidosis

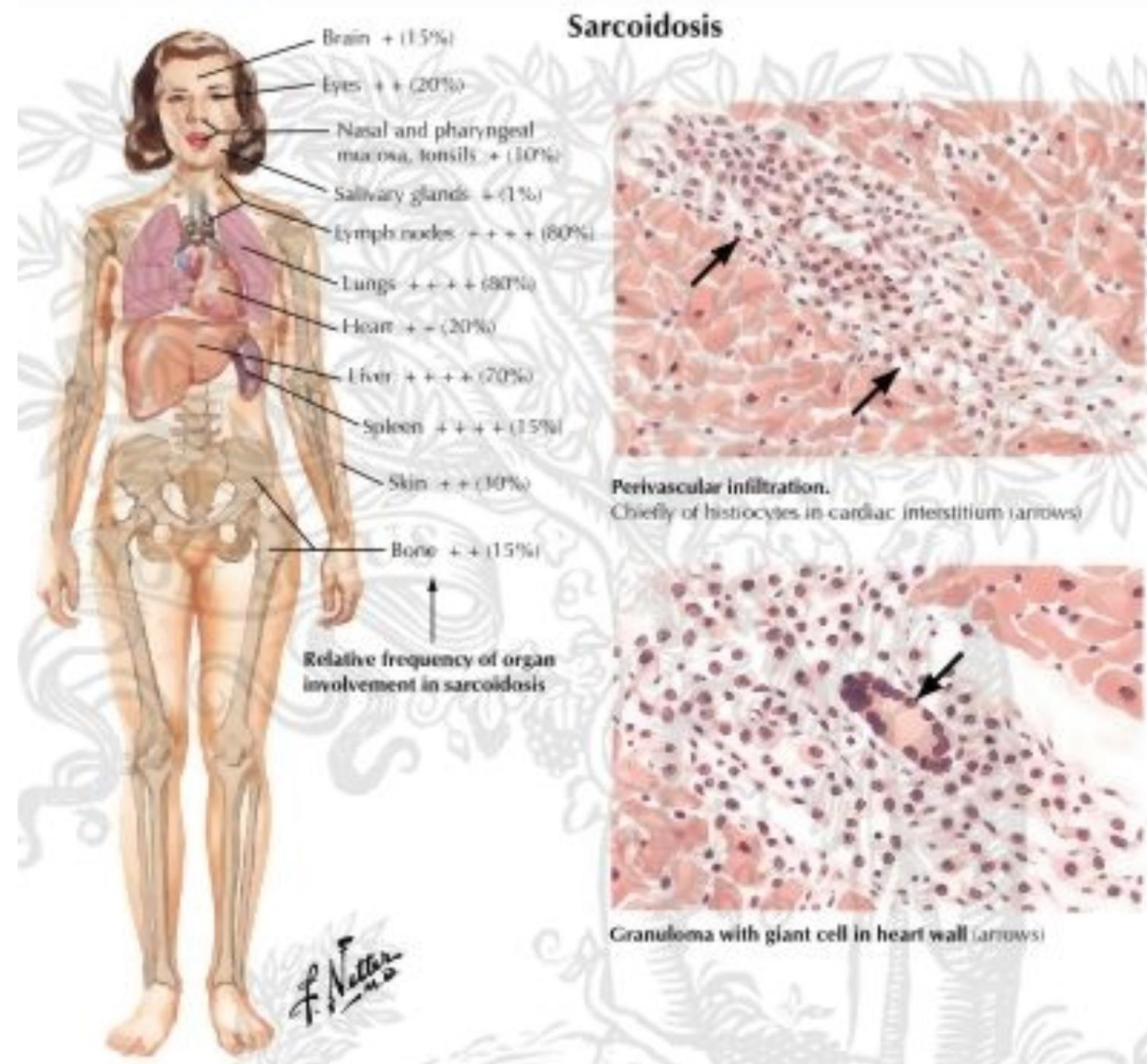
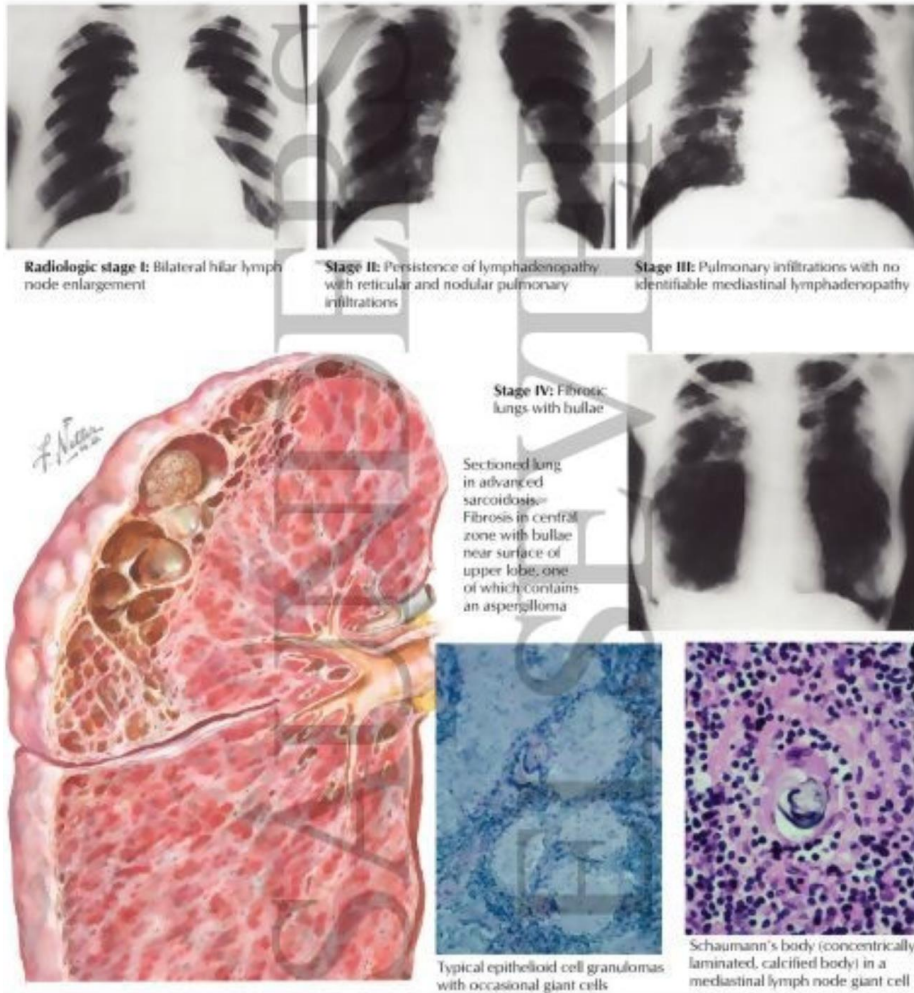


High glycolytic activity in activated macrophages and lymphocytes present in granulomas → FDG uptake.

? Other granulomatous disease ?

Tuberculosis, nontuberculous mycobacteria, fungal infections, foreign bodies (talc, sutures)...

Sarcoidosis



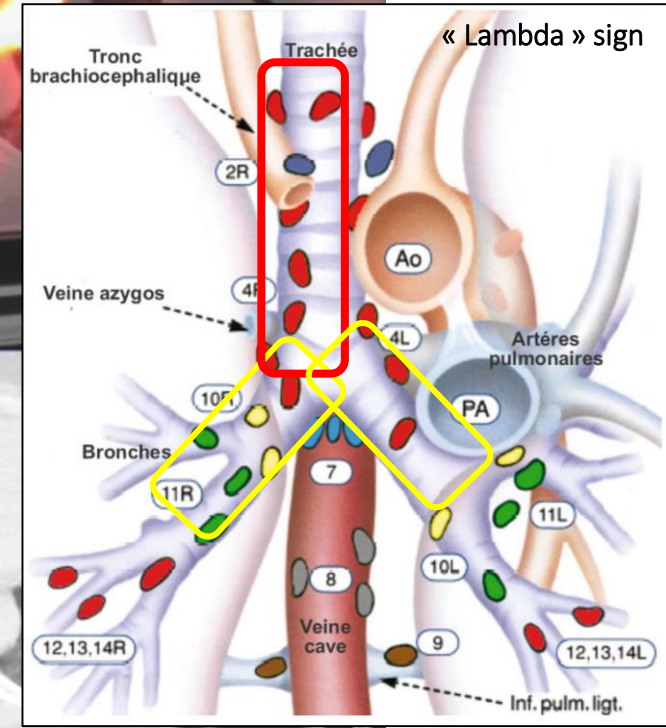
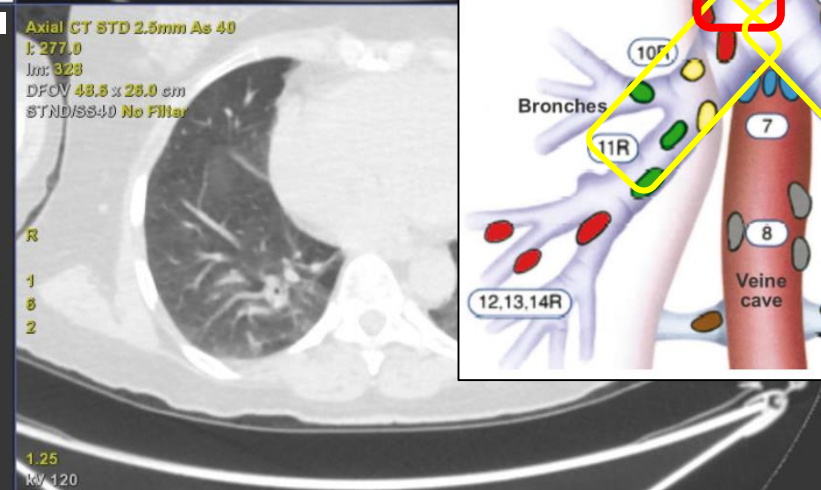
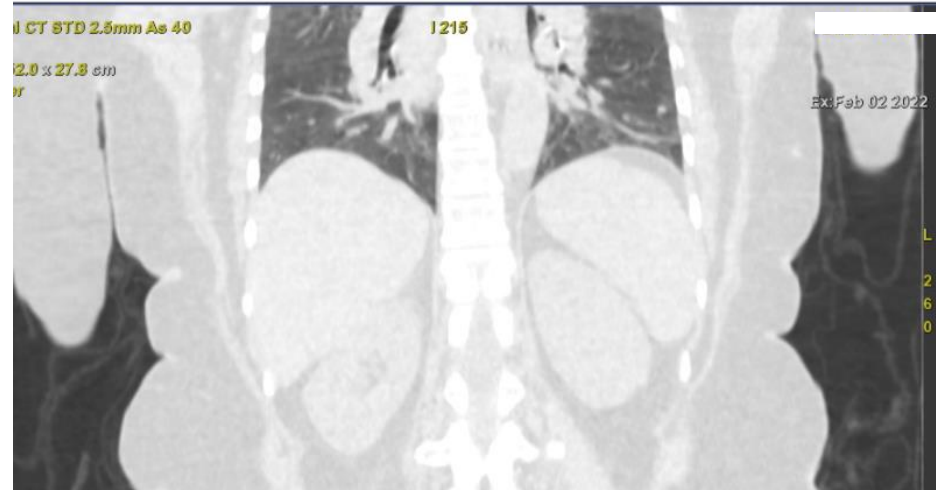
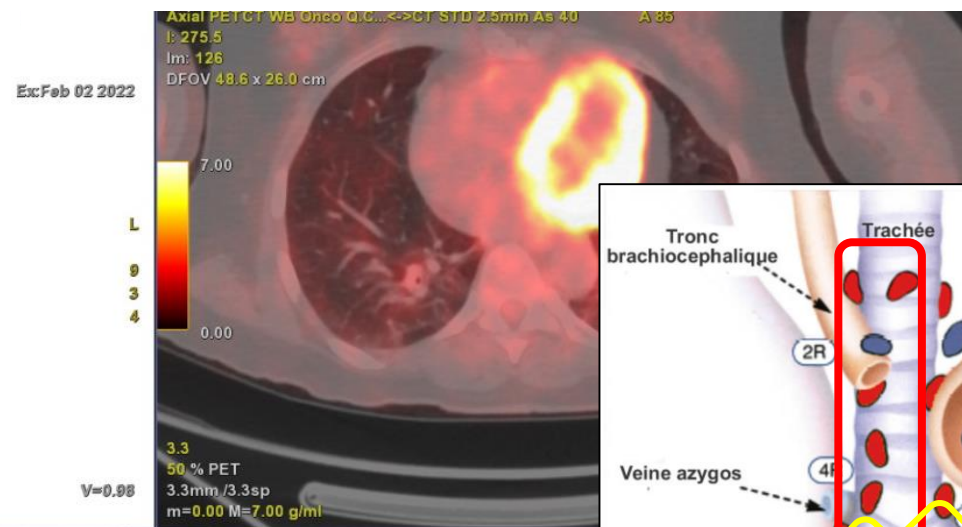
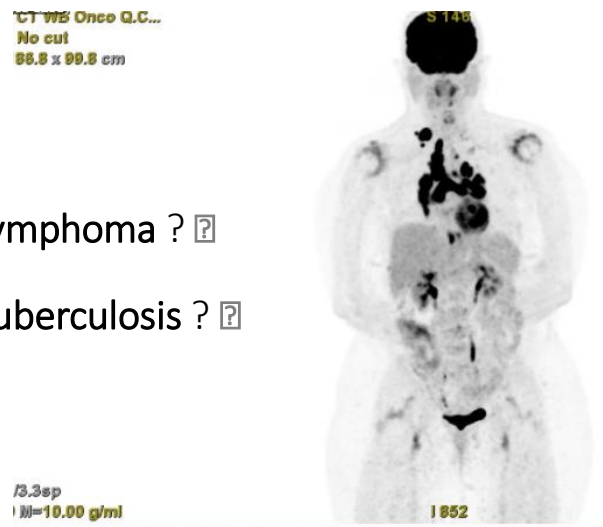
Acquisition FOV should be expanded in specific settings such as involvement of peripheral bones.

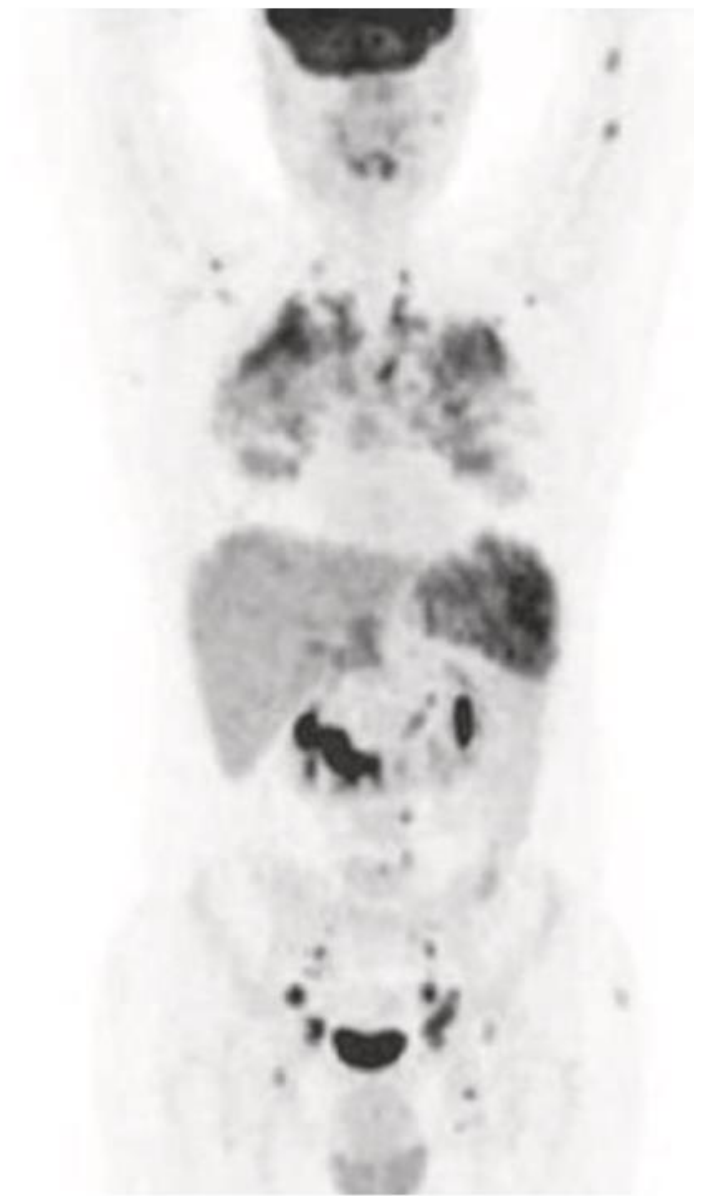
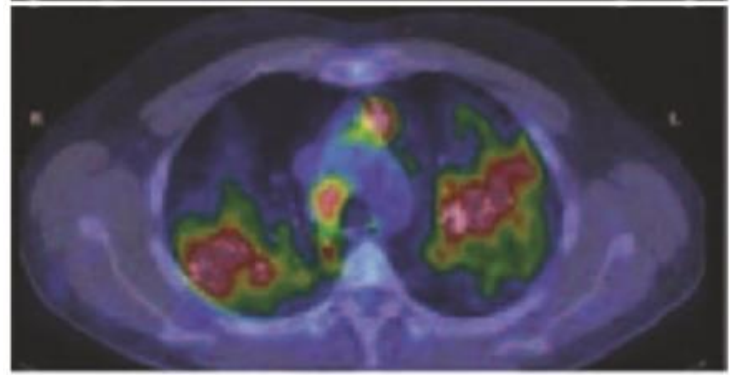
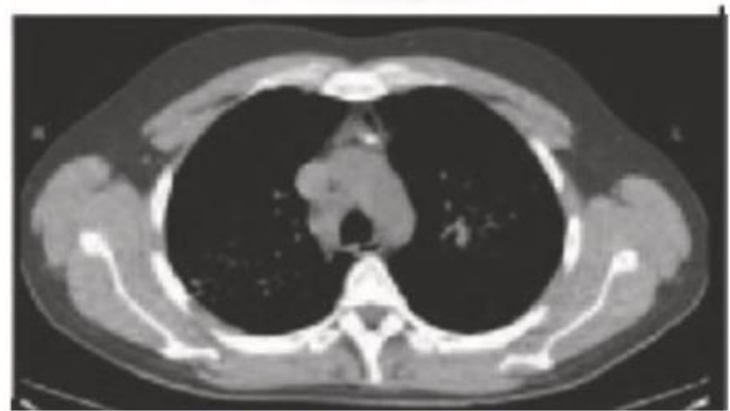


56-year-old woman. Fatigue, dyspnea, CRP 18 mg/L, VS 57 mm/h.

Could it be a lymphoma ? ?

Could it be a tuberculosis ? ?

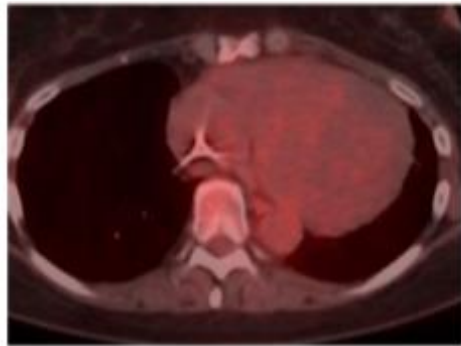
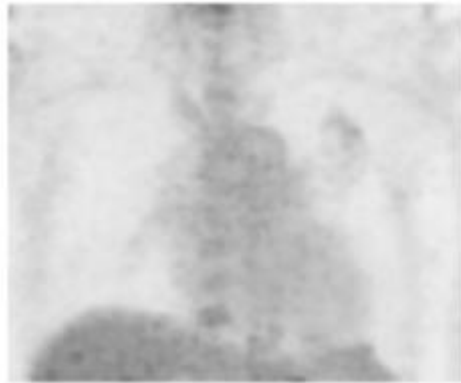




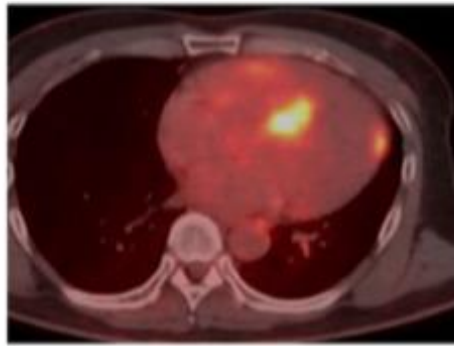
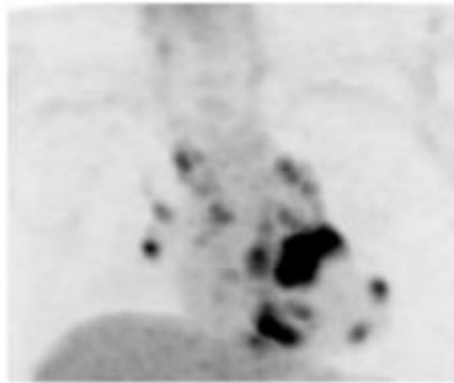


Cardiac sarcoidosis

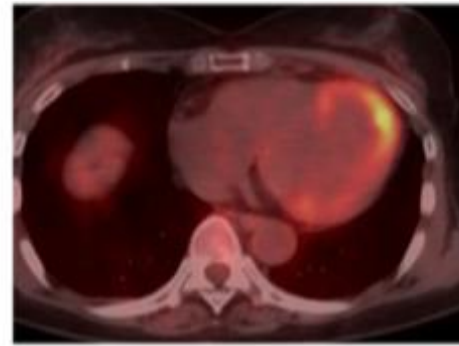
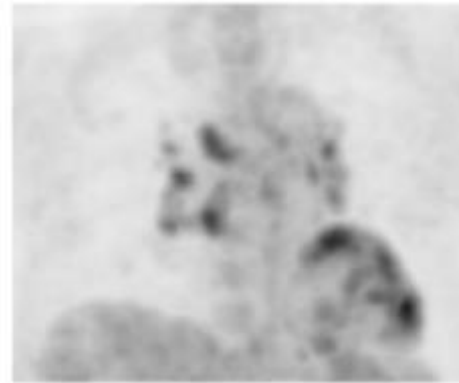
- 5-10% of sarcoidosis cases
- High morbi-mortality (fibrosis → heart block, ventricular arrhythmia, cardiomyopathy)
- Early diagnosis! (treatment : glucocorticoid treatment, CIED)
- Indications of FDG PET/CT
 - Biopsy proven extra-cardiac sarcoidosis with abnormal screening for cardiac involvement.
 - Unexplained new conduction abnormality in patients below the age of 60.
 - Evaluation of treatment response.



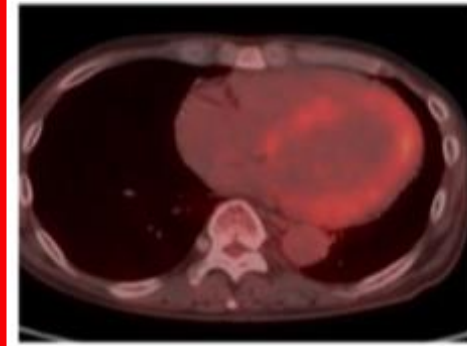
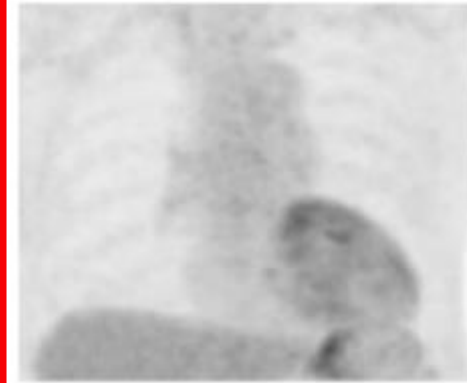
None



Focal



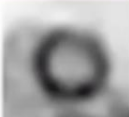
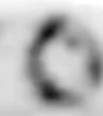
Focal on Diffuse



Diffuse

- Most frequently physiological uptake if :
- Diffuse
 - Isolated homogenous basal lateral wall
 - Papillary muscle
 - Basal 'ring'

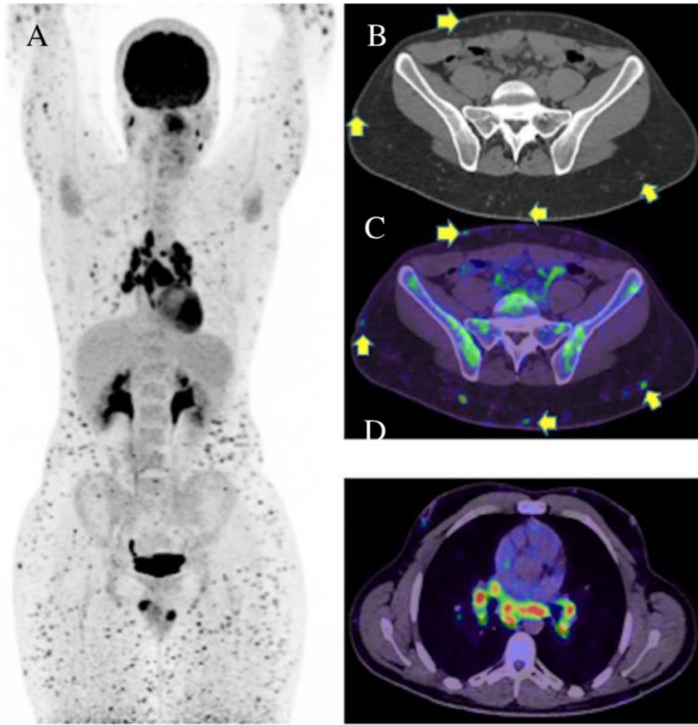
Resting myocardial perfusion imaging should be performed

Rest Perfusion	FDG	Frequency	Example		Interpretation / Comment
			Perfusion	FDG	
Normal perfusion and metabolism					
Normal	Normal (negative)	32 (27%)			Normal
Normal	Diffuse (non-specific)	15 (12%)			Diffuse FDG most likely due to failure to suppress FDG from normal myocardium
Abnormal perfusion <u>or</u> metabolism					
Normal	Focal	20 (17%)			Nonspecific pattern; focal increase in FDG may represent early disease vs. normal variant
Positive	Negative	17 (14%)			Rest perfusion defect may represent scar from cardiac sarcoidosis or other etiologies
Abnormal perfusion <u>and</u> metabolism					
Positive	Focal increase ("mismatch pattern")	23 (19%)			Presence of active inflammation ± scar in the same location
Positive	Focal on diffuse	6 (5%)			Similar to above but also areas of inability to suppress FDG from normal myocardium vs. diffuse inflammation
Positive	Focal increase (different area)	5 (4%)			Presence of both scar and inflammation but in different segments



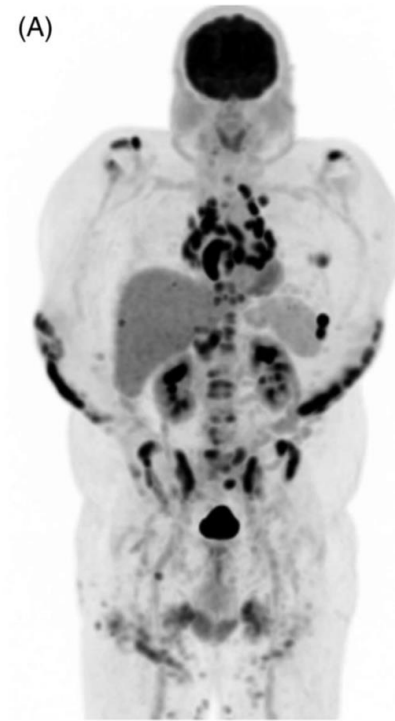
Cutaneous manifestations in sarcoidosis

Other FDG patterns reported in the litterature (... very few !)



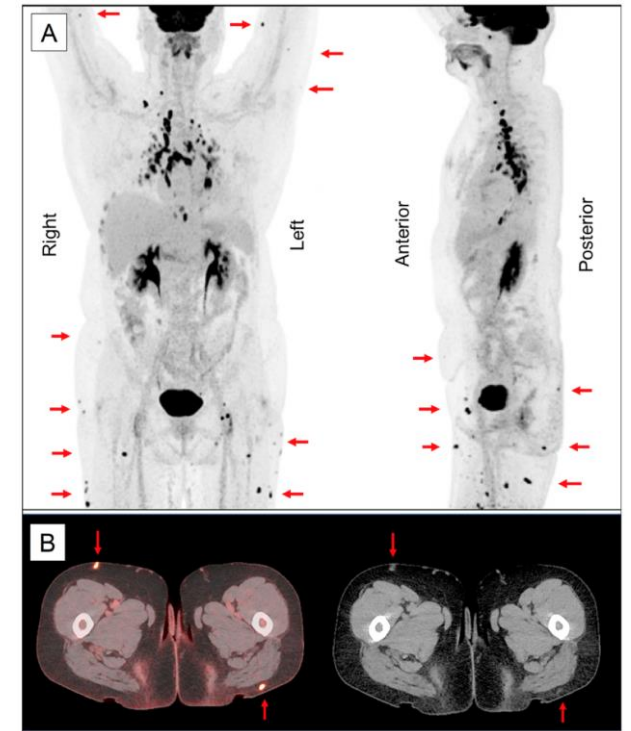
"The snow leopard sign"

Bompard F. Eur J Nucl Med Mol Imaging. 2019



Subcutaneous (Darier-Roussy) nodules

Youn P. Respirol Case Rep. 2022



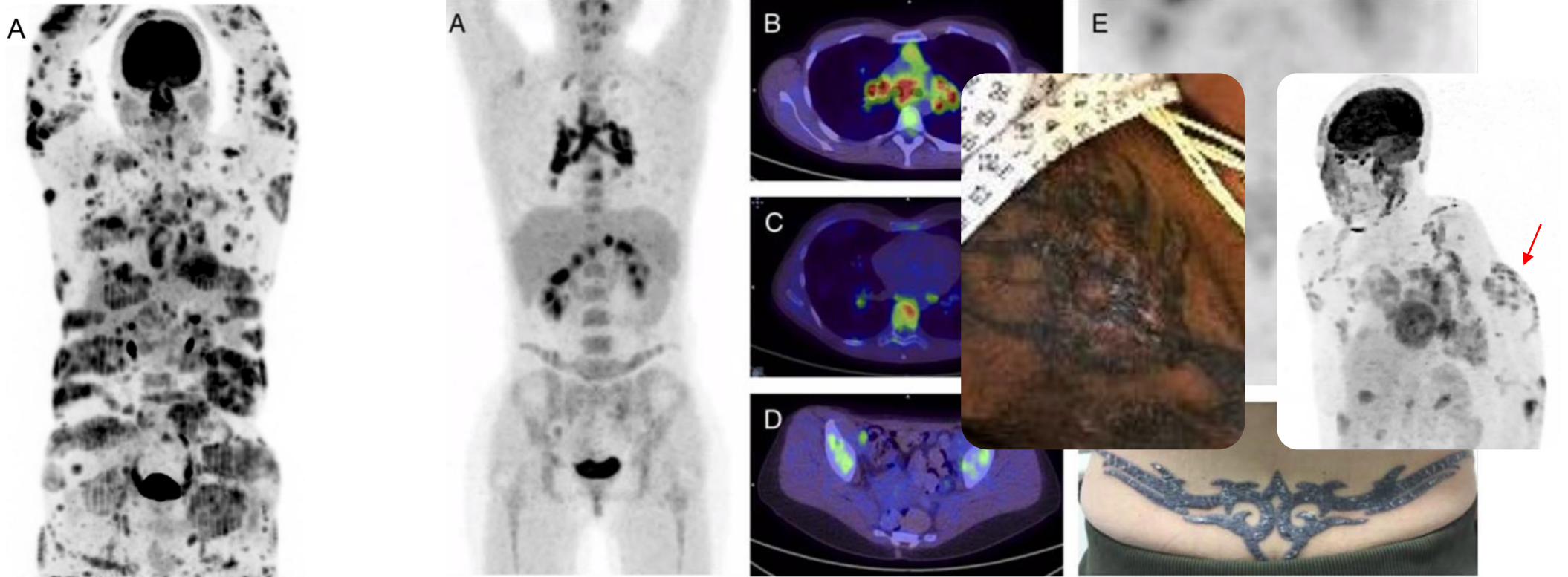
Subcutaneous nodules

Sillanmäki S. J Nucl Cardiol. 2023



Cutaneous manifestations in sarcoidosis

Other FDG patterns reported in the litterature (... very few !)



Diffuse scattered plaques and nodules
Li Y. Clin Nucl Med. 2011

Lesion on lower back tatoo
Grosse J. Clin Nucl Med. 2018



...Be aware



Monkeypox
Manta R. EJNMMI. 2023



Lymphoblastic B lymphoma
(CHU Saint Pierre)



On a side note...



≠



A tiger man (*muscle* involvement of sarcoidosis)

Wieërs G et al. Lancet. 2012



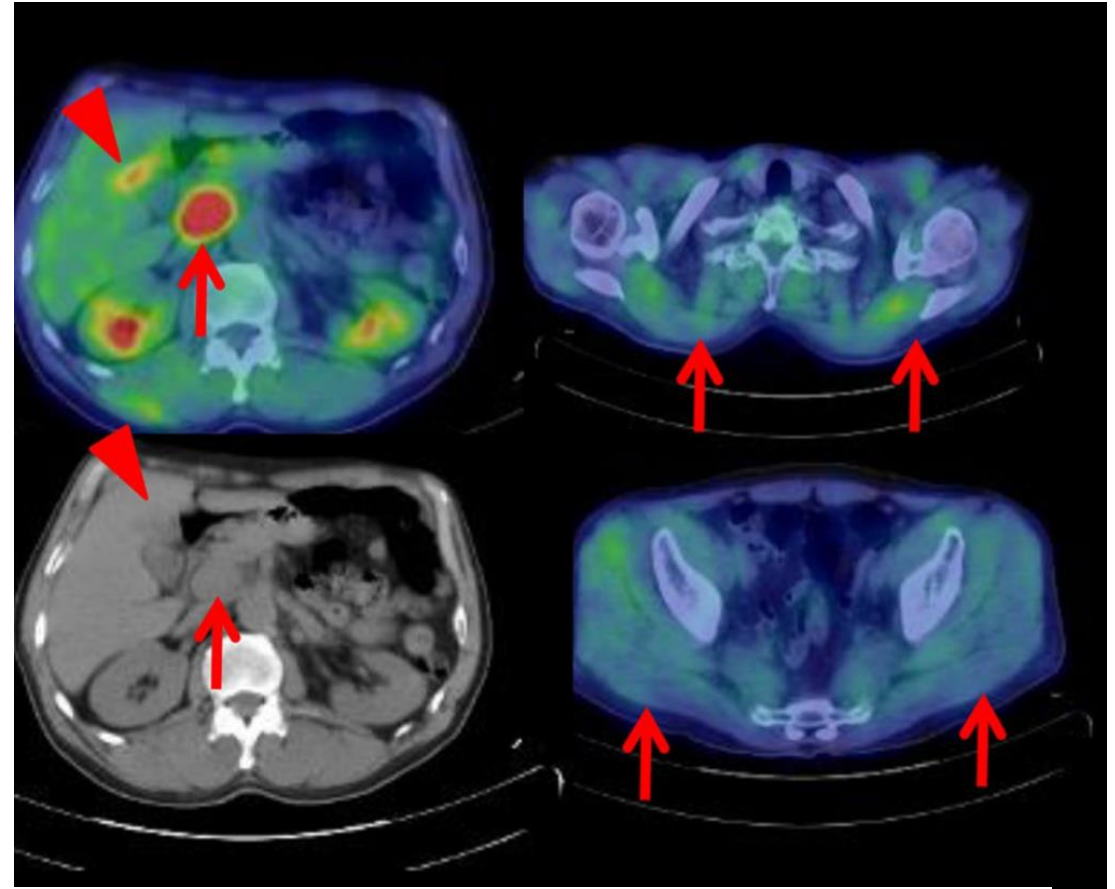
...Be aware



?

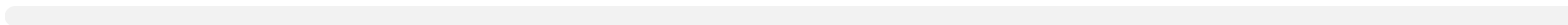


?



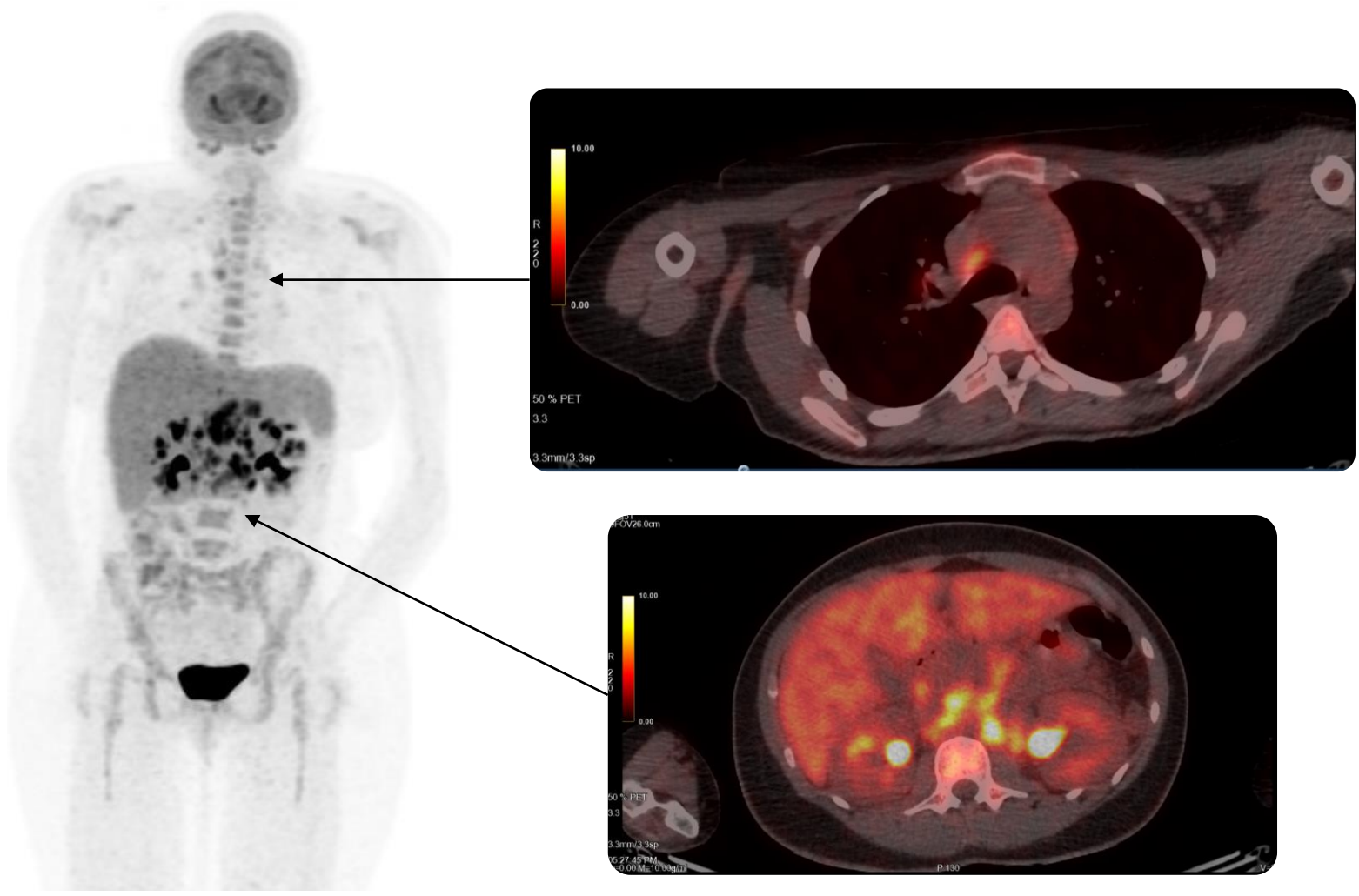


Clinical case





22 year-old woman from Sierra Leone. Fever, night sweat, fatigue. Normal blood smear, CXR, chest CT, blood and urine culture.



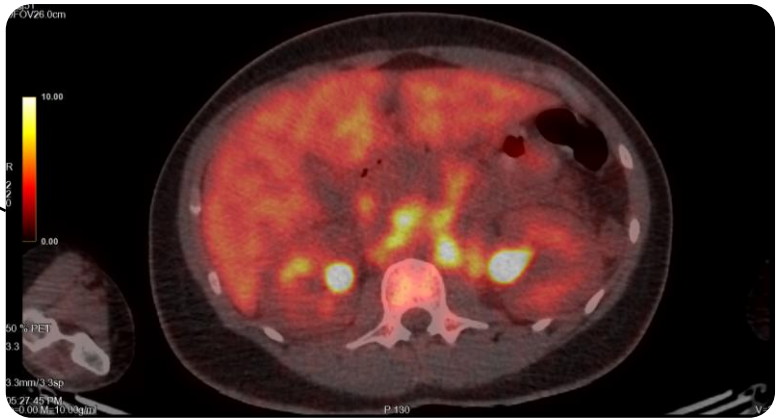


22 year-old woman from Sierra Leone. Fever, night sweat, fatigue. Normal blood smear, CXR, chest CT, blood and urine culture.



Retroperitoneal lymph nodes biopsy (EUS) : necrotic granulomatous adenitis. Zeihl Neelsen+

Antituberculous therapy

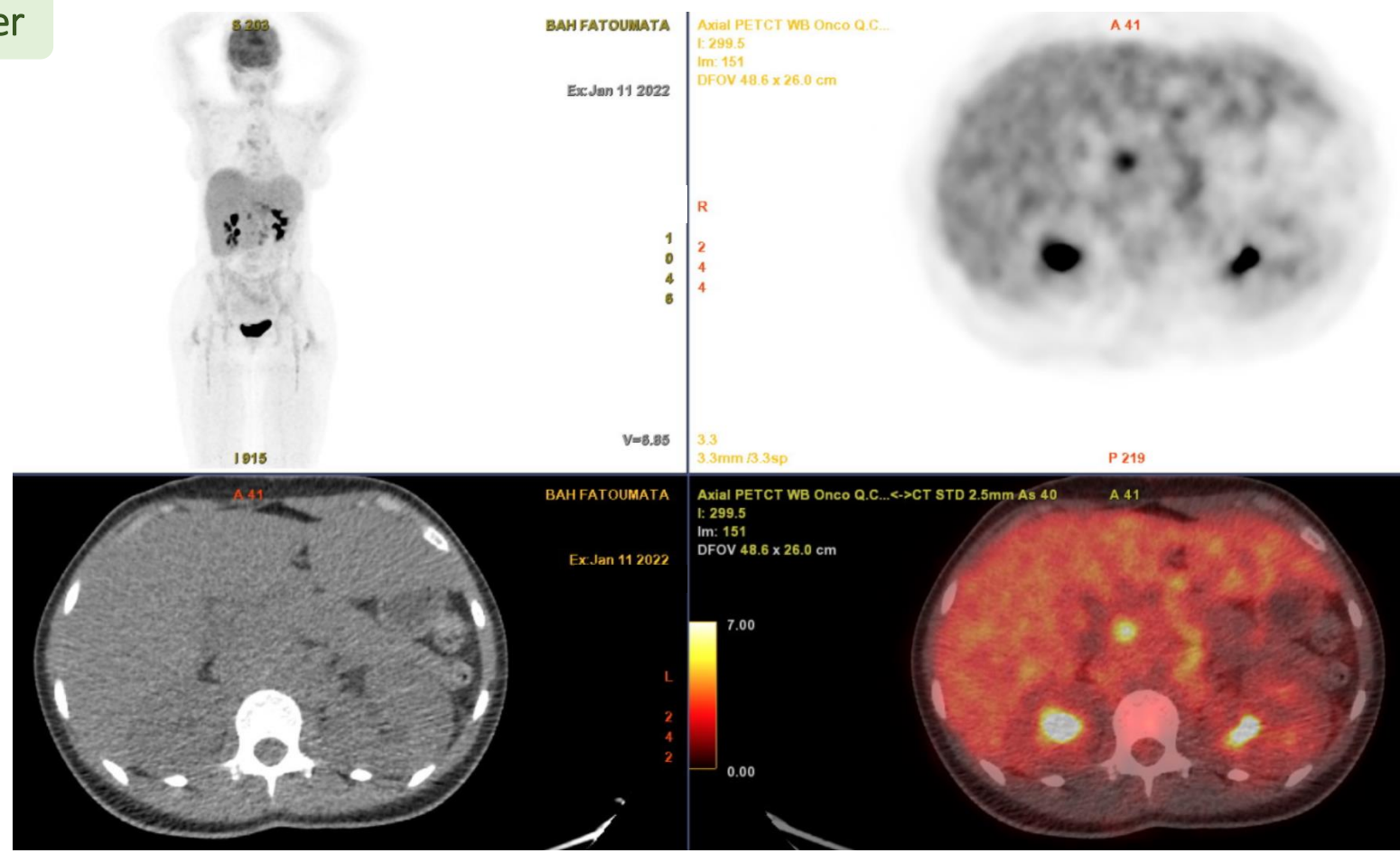




22 year-old woman from Sierra Leone. Fever, night sweat, fatigue. Normal blood smear, CXR, chest CT, blood and urine culture.



Two months later





Tuberculosis

- Nearly two **billion** people are infected with *Mycobacterium tuberculosis*.
 - **Prompt diagnosis** of active TB allows timely therapeutic intervention and minimizes community transmission.
-



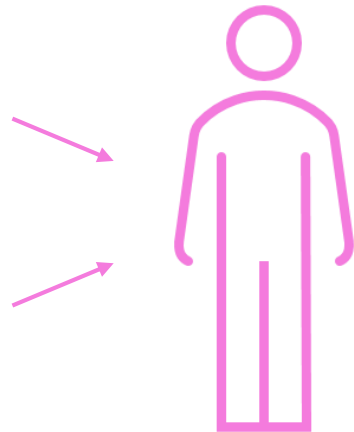
Tuberculosis

Clinical manifestations

Cough, lymphadenopathy, fever,
night sweats, weight loss

Relevant epidemiologic factors

History of prior TB infection
Possible TB exposure
Travel to an area where TB is endemic...





Tuberculosis



Exposure to *Mycobacterium tuberculosis*

Tuberculin skin test

Interferon-gamma release assay (IGRA)

= Tools that measure immune sensitization to TB protein antigens

Conventional imaging

Chest X-Ray

Chest CT (better sensitivity)

Cannot distinguish active from inactive disease

FDG ?

Diagnosis

Microscopic examination, PCR (Gene Xpert), culture

→ From a **bodily secretion** (eg sputum, bronchoalveolar lavage, or pleural fluid) or **tissue** (pleural biopsy or lung biopsy)

FDG ?



Tuberculosis



Treatment

Intensive phase (2 months : RIF, INH, EMB, PNA)



Continuation phase (traditionally 2 drugs for at least 4 additional months)

TB lymphadenitis	4-6 months
Pulmonary TB	6-9 months
Extrapulmonary TB	6-12 months

FDG ?

• **Longer regimen: Indications** – Indications for use of a longer, individualized regimen include (see 'Regimen selection' above):

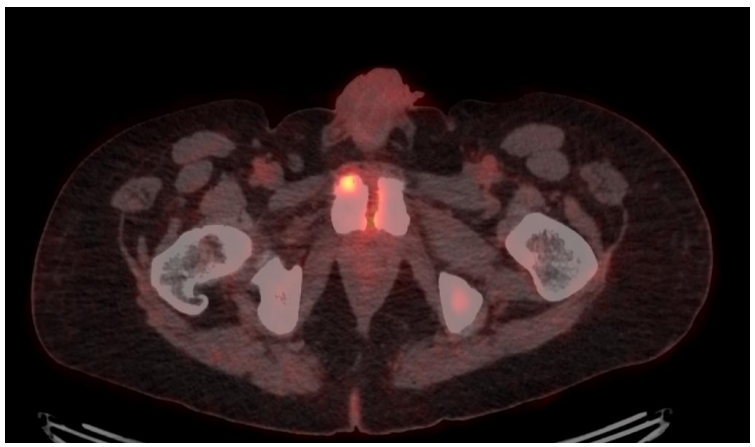
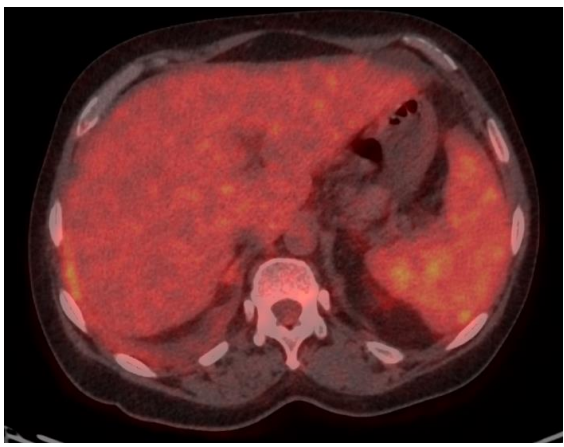
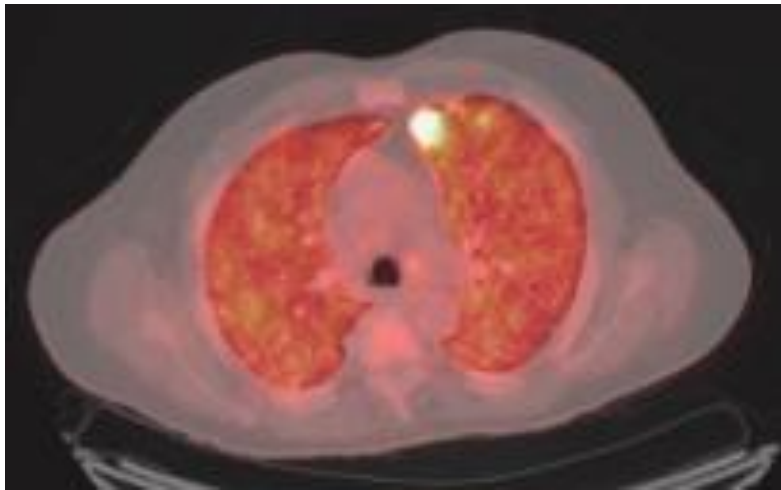
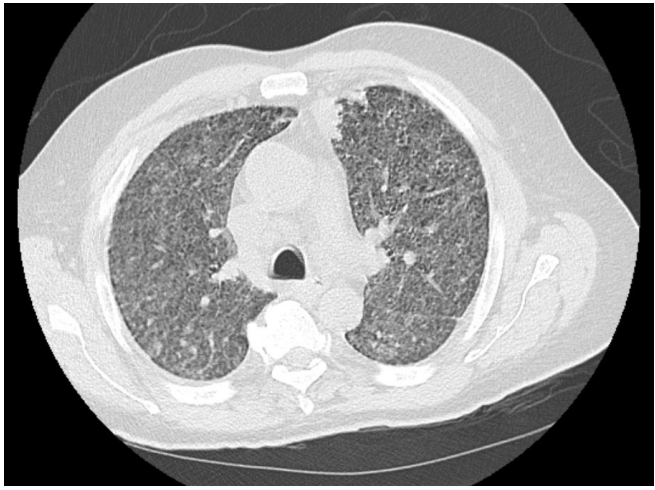
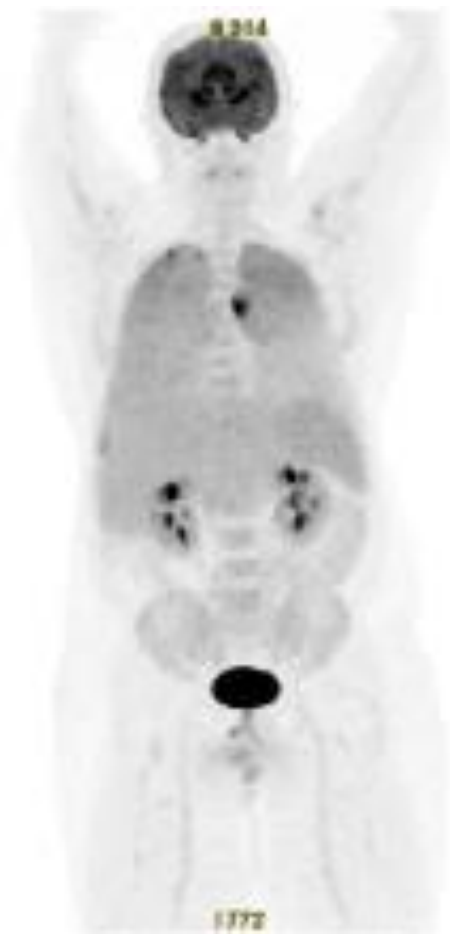
- Disseminated, meningeal, or central nervous system disease
- Patients with advanced HIV infection (CD4<50 cells/microL) and extrapulmonary disease
- Pregnancy
- Extensive (or advanced) TB disease, such as bilateral cavitory disease or extensive parenchymal damage on chest radiography
- Contraindication to one or more drugs in the shorter course regimens

For patients with MDR-TB or XDR-TB in the setting of the above indications, we suggest a longer regimen rather than an abbreviated regimen (**Grade 2C**).

Not well standardized

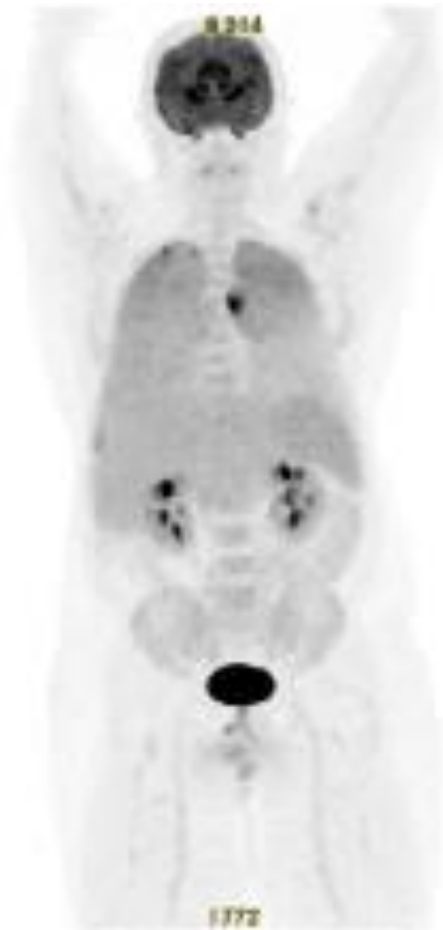


52 year-old man who recently traveled to Cameroun. Dyspnea, dry cough, fever, night sweat and weight loss. CRP 85.9 mg/L.





52 year-old man who recently traveled to Cameroun. Dyspnea, dry cough, fever, night sweat and weight loss. CRP 85.9 mg/L.



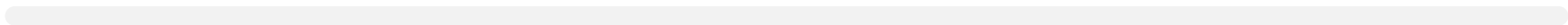
Miliary TB, with pleural and osteoarticular lesion



Antituberculous therapy 12 months (4T 3m + Rif Iso 9m)
Clinical improvement
Normal CXR after 2 months



Osteomyelitis



Osteomyelitis

- Etiologies
 - Direct extension from trauma and/or surgery
 - Hematogenous spread
- Localization
 - **Peripheral**
 - ⚠️ “complicated bone” : post-fracture, post-surgery, diabetic foot, periprosthetic joint infections.
 - **Axial** : spondylodiscitis

❓ Why this classification ?

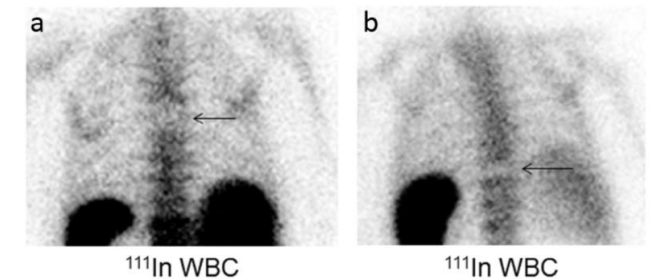
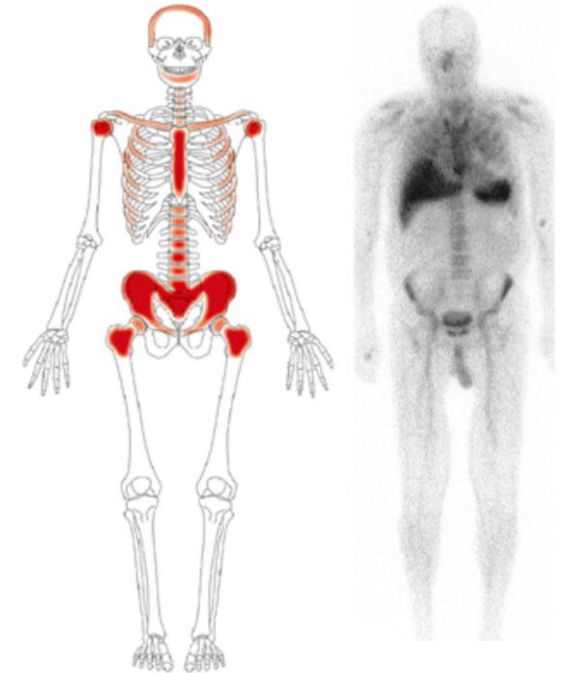
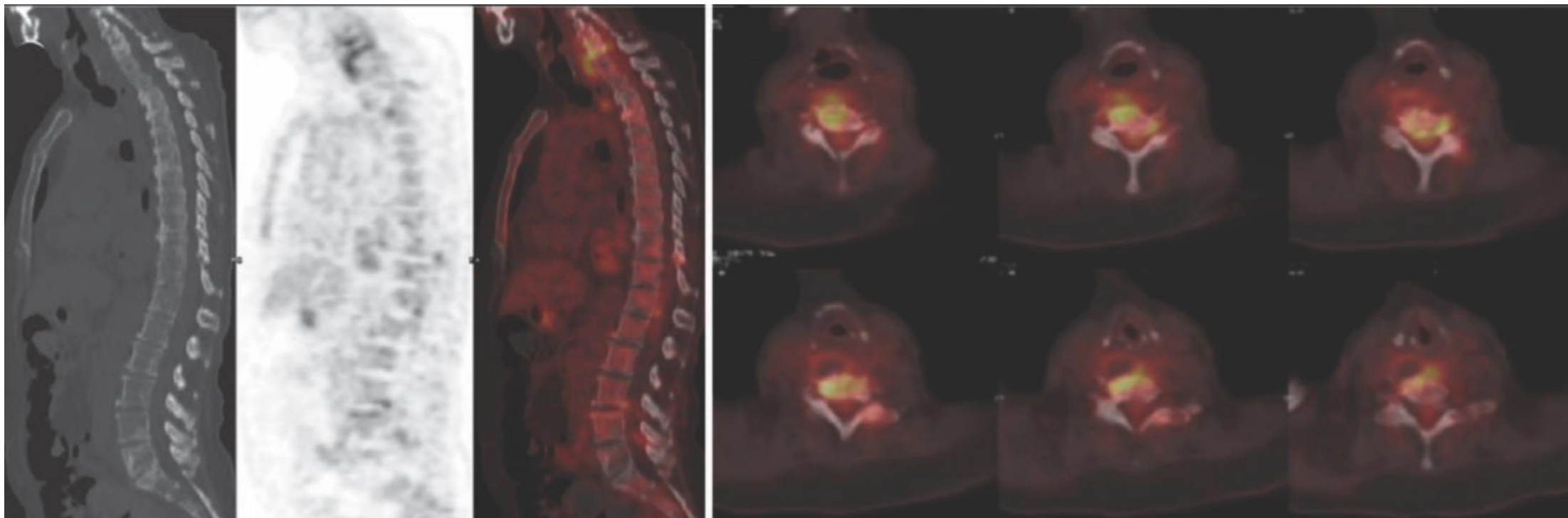


Figure 12 (A) T6 spondylodiscitis. There is an area of decreased labeled leukocyte accumulation (arrow) in the mid-thoracic spine. (B) T10 compression fracture. There is an area of decreased labeled leukocyte accumulation (arrow) in the lower thoracic spine, similar to A. Although more than half of all cases of spondylodiscitis present as decreased activity on labeled leukocyte images, this pattern is not specific for infection.



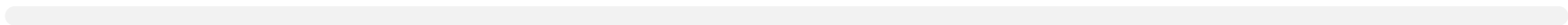
79 year old woman. Fever and Neck pain. Elevated CRP. Positive blood cultures for *staphylococcus aureus*

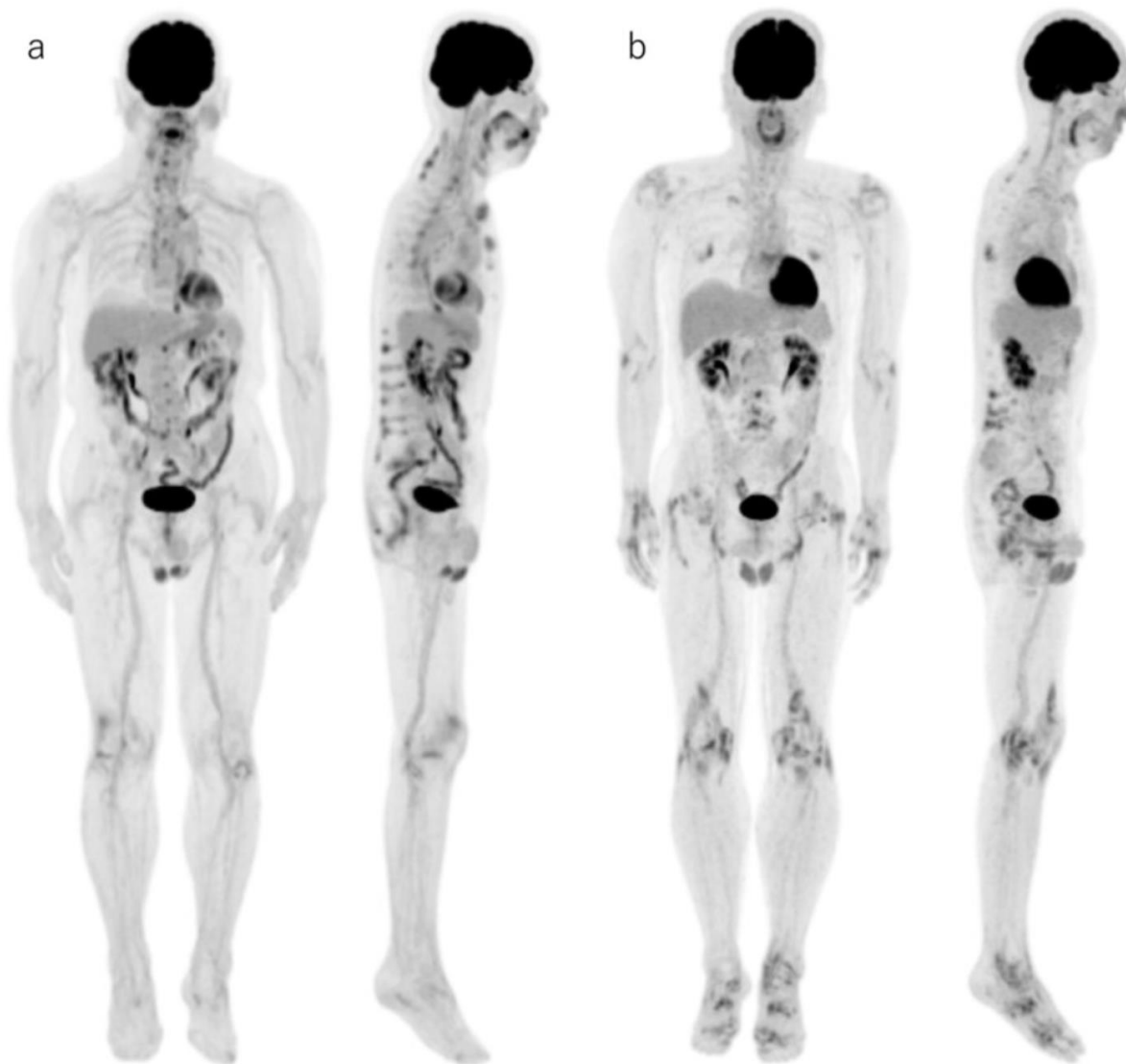
FDG PET/CT





Other inflammatory diseases

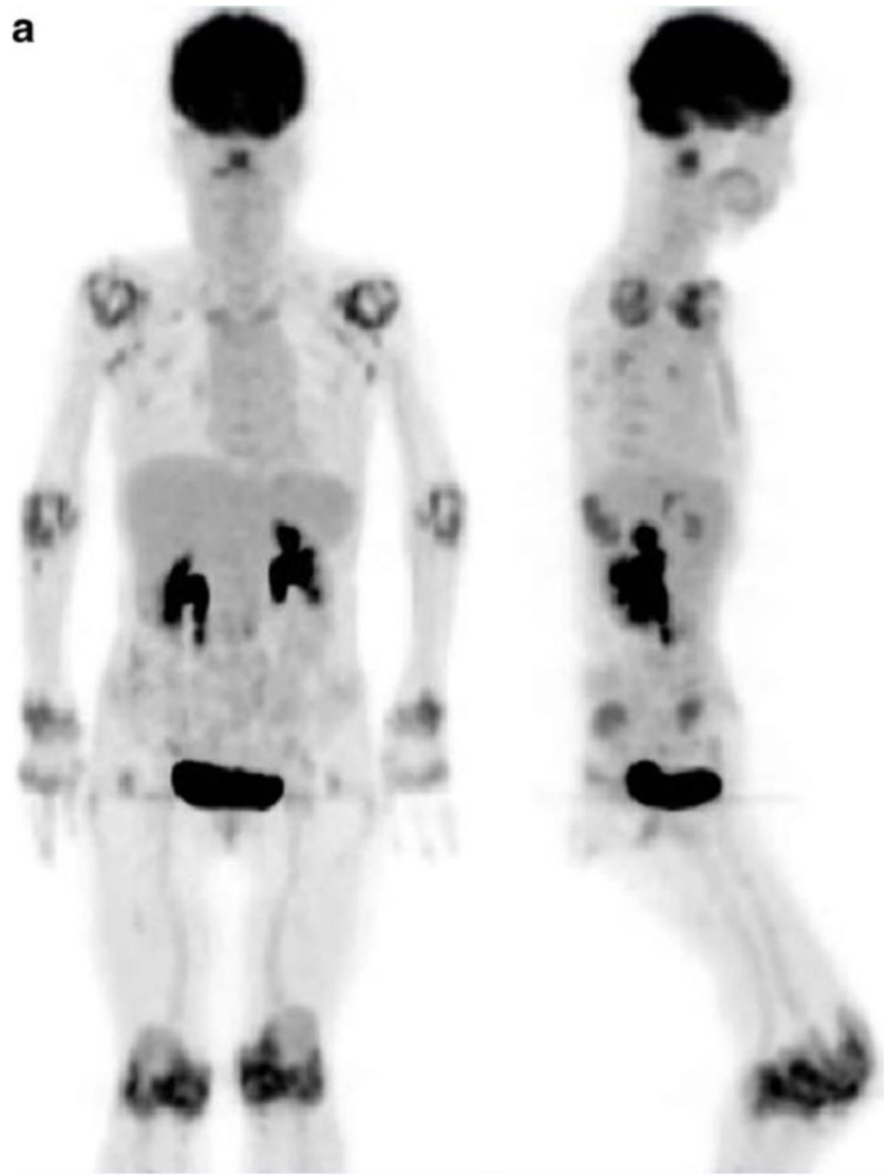




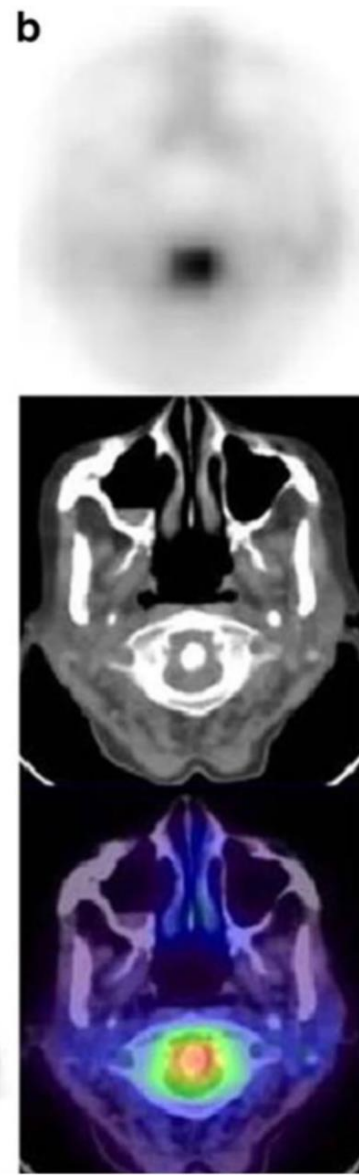
Ankylosing Spondyloarthritis



a



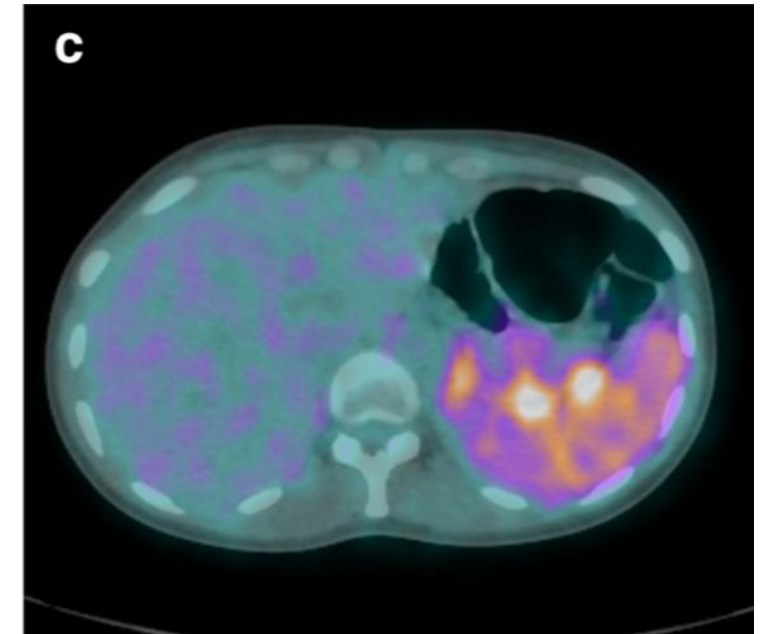
b



Rheumatoid arthritis



Systemic lupus erythematosus



Lymphadenopathy is a common and non-specific feature of SLE (23–34 %)



FDG PET/CT

White Blood Cell Scan

Bone Scintigraphy

High sensitivity	Specific for infection	• High NPV to rule out peripheral osteomyelitis • Not specific : often needs to perform a complementary WBC scan. • Not indicated to rule out PMR (→ FDG)
Not specific for infection	Long delay injection-acquisition (0h-3h-24h) Physiological bone marrow uptake	
• Fever of unknown origin * • Bacteremia/septicemia * • Large vessels vasculitides • Sarcoidosis* • Tuberculosis • Endocarditis (PVE, NVE)* • LVAD and CIED infection* • Vascular prosthesis infection • Spondylodiscitis • AIDS (FUO, Lymphoma, TB , KS...) • ...	• Peripheral osteomyelitis • Joint prosthesis infection • Vascular prosthesis, LVAD and CIED infections • Intra-abdominal infections (¹¹¹In) • Pulmonary, CNS infections ...	
CIED : cardiac implantable electronic devices (pacemakers, implantable cardiac defibrillators, and cardiac resynchronization therapy devices). LVAD : Ventricular Assist Device.		



Thank you for your attention
