Fever of unknown origin: the value of FDG-PET/CT

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Abstract

Fever of unknown origin (FUO) is commonly defined as fever higher than 38.3°C on several occasions during at least 3 weeks with uncertain diagnosis after a number of obligatory investigations. The differential diagnosis of FUO can be subdivided in four categories: infections, malignancies, non-infectious inflammatory diseases, and miscellaneous causes. In most cases of FUO, there is an uncommon presentation of a common disease. FDG-PET/CT is a sensitive diagnostic technique for the evaluation of FUO by facilitating anatomical localization of focally increased FDG uptake, thereby guiding further diagnostic tests to achieve a final diagnosis. FDG-PET/CT should become a routine procedure in the work-up of FUO when diagnostic clues are absent. FDG-PET/CT appears to be a cost-effective routine imaging technique in FUO by avoiding unnecessary investigations and reducing the duration of hospitalization.

Introduction

Fever of unknown origin (FUO) refers to a prolonged febrile illness without an established etiology despite intensive evaluation and diagnostic testing. The exact definition of FUO has been modified over time. In 1961, FUO was defined by Petersdorf and Beeson as an illness of more than three weeks duration with fever higher than 38.3°C (101°F) on several occasions and diagnosis uncertain after one week of study in the hospital [1]. This definition has been changed in 1991 by removing the requirement that the evaluation must take place in the hospital and also by excluding immunocompromised patients, because these patients need a different approach in diagnosis and therapy [2]. Later, the quantitative criterion of diagnosis uncertain after a period of time has been changed to a qualitative criterion that requires a number of diagnostic procedures to be performed [3 4 5]. The current definition of FUO is: 1) temperature ≥38.3°C (101°F) on at least two occasions, 2) duration of illness ≥three weeks or multiple febrile episodes in ≥three weeks, 3) not immunocompromised (defined as neutropenia for at least one week in the three months prior to the start of the fever; known HIV-infection; known hypogammaglobulinemia or use of 10mg prednisone or equivalent for at least two weeks in the three months prior to the start of fever), and 4) uncertain diagnosis despite thorough history-taking, physical examination and the following investigations: erythrocyte sedimentation rate or C-reactive protein, hemoglobin, platelet count, leukocyte count and differentiation, electrolytes, creatinine, total serum protein, protein electrophoresis, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, ferritin, antinuclear antibodies, rheumatoid factor, microscopic urinalysis, three blood

cultures, urine culture, chest X-ray, abdominal ultrasonography, and tuberculin skin test or interferon gamma release assay. FUO is closely related to inflammation of unknown origin (IUO) and causes and workup are the same for both FUO and IUO [6].

The differential diagnosis of FUO can be subdivided in four categories: infections, malignancies, non-infectious inflammatory diseases (NIID), and miscellaneous causes [5 7]. In Western countries, infections accounts for one-fifth of FUO cases, with next in frequency NIID and malignancies. In non-Western countries, infections (mostly tuberculosis) are a much more common cause of FUO (43% versus 17%) with similar cases due to NIID and malignancies [8]. In most cases of FUO, there is an uncommon presentation of a common disease. Important for diagnosing FUO is a search for potentially diagnostic clues (PDCs) in a complete and repeated history-taking, physical examination, and the essential investigations. PDCs are defined as all localizing signs, symptoms, and abnormalities potentially indicating a certain diagnosis. Based on these PDCs, a limited list of probable diagnosis can be made. Further diagnostic procedures should be limited to specific investigations to confirm or exclude these possible diseases, because most investigations are helpful only when performed in patients with PDCs for the diagnosis searched for. When PDCs are absent, FDG-PET/CT should be performed to guide additional diagnostic tests. In case negative FDG-PET/CT and persisting FUO, it is probably more rewarding to wait for new PDCs to appear than immediately performing more screening investigations.

Focal inflammatory and infectious processes can be detected by radiologic imaging techniques, such as CT, MRI, and ultrasound. However, inflammatory and infectious

lesions can remain undetected, as substantial anatomic changes take time to develop and may be absent in an early phase. Distinction between active foci and residual changes due to cured processes or surgery is a limitation of these techniques. Also, these imaging techniques routinely provide information only on a part of the body.

For FDG-PET, FDG accumulates in cells with an increased rate of glycolysis. All activated leukocytes (granulocytes, monocytes, and lymphocytes) demonstrate increased FDG uptake and delineation of acute and chronic inflammatory and infectious processes. The mechanism of FDG uptake in these activated leukocytes is related to the usage of glucose as the primary energy source only upon activation during the metabolic burst of these cells. FDG-PET can be used to evaluate disease throughout the body, but has limitations for assessment of the urinary tract due to FDG excretion into the urine, of the brain due to high accumulation of FDG, and potentially of the gastrointestinal tract due to diffuse or focal uptake as a result of peristalsis. In patients with fever, bone marrow uptake is frequently increased because of nonspecific activation of proliferating bone marrow cells due to interleukin-dependent up regulation of glucose transporters [9]. In the myocardium, accumulation of FDG may be observed, which can be decreased by using a prior low carbohydrate fat allowed diet [10 11] and additional heparin preadministration [12].

Compared to conventional scintigraphic techniques, FDG-PET has the advantages of higher resolution, higher sensitivity in chronic low-grade infections, and high accuracy in the central skeleton, as well as the short time period between injection of the radiopharmaceutical and the moment of imaging [13]. Important disadvantages of

conventional scintigraphic methods, such as ^{67}Ga-citrate scintigraphy and ^{111}In-labeled or ^{99m}Tc-labeled leukocyte scintigraphy, are handling of potentially infected blood products (labeled leukocyte scintigraphy), high radiation burden (^{111}In-labeled leukocyte and ^{67}Ga-citratescintigraphy), instability of the labeling (^{99m}Tc-labeled leukocyte scintigraphy), and the relatively long timespan between injection and diagnosis (^{67}Ga-citrate scintigraphy).

Improved anatomical resolution by direct integration with CT (FDG-PET/CT) has further boosted the accuracy of FDG-PET/CT. Because FDG-PET/CT provides whole-body imaging in a single session with a relatively low radiation exposure, it plays an important role in the diagnosis of patients with FUO in clinical practice. Many studies on the value of FDG-PET and FDG-PET/CT in diagnosis of FUO have been published, often referring to the effectiveness of these imaging techniques in terms of sensitivity, specificity, and clinical helpfulness. However, calculating sensitivity and specificity in patients with FUO is difficult or even misleading due to the lack of a true gold standard. Also, in a relatively high number of patients, a final diagnosis cannot be established and nonspecific FDG-uptake could lead to false-positive findings and to shortcomings in follow-up of these findings. Therefore, in FUO it is more useful to investigate the clinical helpfulness of FDG-PET and FDG-PET/CT rather than sensitivities and specificities [9]. FDG-PET/CT is helpful when the FDG-PET/CT contributes to the final causal diagnosis of FUO.

FDG-PET/CT in FUO in adults

Before introduction of PET/CT, the value of stand-alone FDG-PET (without combined CT) has been studied in patients with FUO [14-22] [23]. These studies showed FDG-PET

to be a valuable diagnostic technique in patients with FUO with a helpfulness of FDG-PET in 16-69% of patients. Figure 1 shows an example of an FDG-PET/CT in a patient with FUO due to non-infectious vasculitis of the large arteries, subsequently treated with cortoicosteroids. Figure 2 depicts the FDG-PET/CT of a septic patient due to vascular graft infection, treated with a prolonged course of antibiotics. However, comparing these studies was rather difficult, due to a different definition of FUO in these studies and also in some studies a (highly) selected patient population. In general, in these studies, FDG-PET was often performed without using a structured diagnostic protocol, and therefore at different stages of the process of FUO. Bleeker-Rovers et al. [5] have already shown that using such a structured diagnostic protocol including FDG-PET reduces the chance of selection bias.

After the introduction of FDG-PET combined with CT, the diagnostic value of FDG-PET/CT has been investigated in one prospective study and in 15 retrospective studies in 823 patients with FUO (Table 1) [24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39].The only prospective study on the value of FDG-PE/CT performed in patients with FUO is the study of Keidar et al. [24]. In this study, 48 patients were included. FDG-PET/CT identified the underlying etiology of FUO in 22 patients (46%). FDG-PET/CT contributed clinically important information to the diagnosis of exclusion of a focal etiology in 90% of cases. Balink et al. [25] retrospectively included 68 patients with FUO. FDG-PET/CT was helpful in 56% and in 93% of positive studies, FDG-PET/CT led to the causal source of FUO either by identifying the etiology of the FUO or by guiding further management, including invasive therapeutic procedures. Federici et al. [26] investigated the value of FDG-PET/CT in ten patients with FUO and four patients with unexplained inflammatory syndrome without fever. FDG-PET/CT was

helpful in 50% of patients with FUO. Ferda et al. [27] performed a retrospective study on 48 patients with FUO. The authors concluded FDG-PET/CT to be helpful in 54% of cases. The study of Kei et al. [28] in 12 patients with FUO showed FDG-PET/CT to be helpful in 42%. Sheng et al. [29] included 48 patients with FUO and FDG-PET/CT was helpful in 67% of cases. In 36 patients (75%), a final diagnosis was established and in 89% of these patients FDG-PET/CT contributed to this diagnosis. The study on 24 patients with FUO of Pelosi et al. [30] showed FDG-PET/CT to be helpful in 46%. Pedersen et al. [31] retrospectively included 22 patients with FUO. In these patients, FDG-PET/CT successfully identified the cause of FUO in 45%. Crouzet et al. [32] investigated the value of FDG-PET/CT in 79 patients with FUO. Overall, FDG-PET/CT was helpful in 57%. Of all patients with a final diagnosis, FDG-PET/CT contributed to the final diagnosis in 74%. The retrospective study of Kim et al. [33] in 48 patients with FUO, showed FDG-PET/CT to be helpful in 52%. An Indian retrospective study on 103 patients with FUO of Manohar et al. [38] investigated the role of FDG-PET/CT and concluded FDG-PET/CT to be helpful in 60% of patients. Of all 63 patients with a final diagnosis, FDG-PET/CT contributed to this diagnosis in 98% of these patients. Tokmak et al. [34] retrospectively included 21 patients with FUO and in these patients FDG-PET/CT was helpful in 60%. Buch-Olsen et al. [39] showed FDG-PET/CT to be helpful in 53% of 57 patients with FUO. Singh et al. [35] included 47 patients with FUO and FDG-PET/CT was helpful in 38% of patients. In this study, a final diagnosis could be established in 53% of patients. The largest retrospective study performed on the value of FDG-PET/CT in FUO is of Gafter-Gvili et al. [37] including 112 patients with FUO. The authors concluded FDG-PET/CT to be helpful in 46% of all patients. Recently, Pereiria et al. [36] investigated the role of FDG-PET/CT in 76 patients of FUO. FDG-PET/CT was helpful in 60% of patients. Overall clinical

helpfulness of all studies investigating FDG-PET/CT in FUO, corrected for study population, was 55%. Recently, Hung et al. [40] retrospectively included 58 patients with FUO who both underwent FDG-PET/CT and ^{67}Ga-SPECT/CT within 7 days from each other. FDG-PET/CT was helpful in 57% of patients versus 33% for ^{67}Ga-SPECT/CT (p<0.05).

As in studies on the value of FDG-PET, comparing these studies is difficult. The definition of FUO was not further specified in six studies [25 27 29 30 32 33 39]. In general, the exact definition of FUO varies in all studies (Table 1). In the study of Pereira et al., immunocompromised patients were also included [36], although these patients need a different approach and are difficult to compare with non-immunocompromised patients with FUO. In most studies no follow-up term was mentioned. Also, because the majority of these studies were retrospective, inclusion bias cannot be excluded as patients with negative findings on conventional imaging techniques are more likely to undergo FDG-PET/CT than patients with positive findings. The difference in timing of FDG-PET/CT as well as the selection of patients could affect the calculation of clinical helpfulness.

FDG-PET/CT in children with FUO

The value of FDG-PET/CT has also been studied in children with FUO. Jasper et al. investigated the value of 47 FDG-PET scans and 30 FDG-PET/CT in 69 children with FUO [41]. The mean age of these children was 8.1 years (range 0.2-18.1 years). Of the 30 FDG-PET/CT scans performed, 17 scans were performed because of FUO and 13 scans were performed because of inflammation of unknown origin without fever. Of the 17 FDG-PET/CT scans performed because of FUO, 24% of FDG-PET/CT

scans were helpful. Of 13 FDG-PET/CT scans performed in IUO patients, 46% of FDG-PET/CT scans were helpful. In a retrospective study of 31 children with FUO, Blokhuis et al. analyzed three FDG-PET scans and 28 FDG-PET/CT scans [42]. The mean age of the children was 8.1 years with a range of 0-16 years. FDG-PET/CT was helpful in 29% (8 out of 28 FDG-PET/CT scans). Chang et al. performed a retrospective study in 19 critical ill children with FUO who required intensive care support. The mean age of the children was 5.7 years (range 0-14 years) [43]. All patients underwent FDG-PET/CT and FDG-PET/CT was helpful in 84% of children. Of 16 children with final diagnosis of FUO and helpful FDG-PET/CT, 9 diagnoses (56%) were infectious, 2 (13%) were NIID related, 3 (19%) were malignancy related, and 2 (13%) were miscellaneous.

Comparing these studies is again difficult as they used a different definition of FUO. Also, Jasper et al. considered some of the negative FDG-PET/CT results useful [41], although a negative FDG-PET/CT scan is only helpful in excluding focal disease, but does not contribute to the diagnosis of the underlying cause of the fever. The children in the study of Chang et al. underwent aggressive diagnostic and imaging workup due to their critical illness, which could declare the high proportion of helpful FDG-PET/CT scans [43].

FDG-PET/CT in FUO in specific patient groups

The value of FDG-PET/CT in FUO has also been investigated in specific patient groups. Although immunocompromised patients were excluded of the classic definition of FUO, two studies investigated the role of FDG-PET/CT in HIV-positive patients with prolonged fever. Castaigne et al. retrospectively studied ten patients

with HIV-associated prolonged fever who underwent FDG-PET/CT [44]. In nine out of these ten patients, FDG-PET/CT was helpful. Tuberculosis was diagnosed in six patients and three patients had a neoplasm (lymphoma in two patients, Kaposi's sarcoma in one patient). Mean CD4 count in these patients was 128 cells/ml (range 13-400 cells/ml). A prospective study of 20 HIV-positive patients with prolonged fever compared with ten HIV-positive asymptomatic but viraemic patients was performed by Martin et al [45]. Mean CD4 count in patients with prolonged fever was 60 cells/ml (range 1-566) and 268 cells/ml (range 209-335) in patients without prolonged fever. Both patient groups underwent FDG-PET/CT. In the HIV-positive patients with prolonged fever, FDG-PET/CT was abnormal in all patients. Sixteen patients (80%) had focal lesions on FDG-PET/CT: eight patients were diagnosed with tuberculosis, three patients had lymphoma, three patients had nontuberculous mycobacteriosis, one patient had a pneumococcal infection, and one patient had dental infection. The four patients without focal FDG-uptake had drug-induced fever (three patients) and visceral disseminated leishmaniasis (one patient). All 20 HIV-positive patients with prolonged fever had abnormal FDG-uptake in peripheral or central lymph nodes. Of all ten HIV-positive patients without prolonged fever, FDG-PET/CT was abnormal in nine patients with hyper metabolic peripheral lymph nodes in all nine patients. SUVmax of peripheral lymph nodes of patients with fever was significantly higher compared to SUVmax in patients without fever. These studies showed that FDG-PET/CT could be helpful in HIV-positive patients with prolonged fever.

FDG-PET/CT has been studied in patients on hemodialysis. A retrospective study investigated the value of FDG-PET/CT in 20 patients on dialysis with prolonged fever [46]. FDG-PET/CT was helpful in 75% of patients.

FDG-PET/CT and CRP levels in FUO

Bleeker-Rovers et al. showed that FDG-PET (without combined CT) did not contribute to the final diagnosis of FUO in case of normal C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) [20]. In a large retrospective study on 498 patients with FUO and inflammation of unknown origin, the predictive value of CRP and ESR to a positive FDG-PET/CT result was determined [47]. ESR values were available in 72% of patients, CRP values were available in all patients. A final diagnosis was established in 331 of 498 patients and FDG-PET/CT had a diagnostic accuracy of 89%. In this study, no optimal cutoff value for CRP could be made. Elevated CRP levels reflected the presence and degree of inflammation more truly compared to ESR levels. FDG-PET/CT was 100% true negative only in patients with CRP levels less than 5 mg/l. Another retrospective study on 76 patients with FUO showed FDG-PET/CT to be helpful and contributory for the diagnosis of FUO when patients had higher levels of CRP and ESR [48]. A recent retrospective study on 223 FDG-PET/CT scans performed in 151 patients with FUO showed an overall helpfulness of FDG-PET/CT in 24.1% of all patients. The presence of fever on the day of FDG-PET/CT or the presence of elevated CRP within seven days before FDG-PET/CT increased the diagnostic value significantly to 70 % and 47 %, respectively (data on file).

Cost-effectiveness of FDG-PET/CT in FUO

Given the large number of FDG-PET/CT studies in patients with FUO, it is of interest to assess the cost-effectiveness of FDG-PET/CT in FUO patients. One Spanish study has been published on the cost-effectiveness of FDG-PET/CT in FUO [49]. In this study on 20 patients, the mean cost per patient of the diagnostic procedures preceding

FDG-PET/CT was €11,167, including an average of 11 days of hospitalization and outpatient checks. If FDG-PET/CT had been performed earlier in the diagnostic process, €5,471 per patient would have been saved on diagnostic tests and hospitalization days. Besides this study, one cost-effectiveness pilot study on FDG-PET/CT in patients with inflammation of unknown origin has been published [50]. In this retrospective study, 46 patients with inflammation of unknown origin who underwent FDG-PET/CT were compared with 46 patients with inflammation of unknown origin without FDG-PET/CT. In patients who underwent FDG-PET/CT, a final diagnosis was established in 32 patients (70%). Estimated mean cost per patient of all diagnostic procedures with FDG-PET/CT was €1,821. When adding the cost of mean number of hospitalization days per patient (6.9 days, range 0-32 days), the mean cost increased to €5,298 per patient. In patients without FDG-PET/CT, a diagnosis was reached in 14 patients (30%). Estimated mean cost per patient of all diagnostic procedures without FDG-PET/CT was €2,051. When adding the cost of mean number of hospitalization days per patient (21 days, range unknown), the mean cost increased to €12,614 per patient. It was concluded that FDG-PET/CT has the potential to become a cost-effective routine imaging technique for further diagnostic decision making by avoiding unnecessary, invasive and expensive investigations and by reducing the duration of hospitalization. An important limitation of this study was the fact that the patient group without FDG-PET/CT was a published dataset from a French study. So the patient groups were selected in different time periods and also in different countries which inevitably led to selection bias. However, an important conclusion was the significantly higher mean cost per patient and also the longer duration of hospitalization in the patient group without FDG-PET/CT compared to patients who did undergo FDG-PET/CT.

Conclusions

FDG-PET/CT is a helpful technique in diagnosing FUO in both adults and children. Therefore, FDG-PET/CT should become a routine procedure in the work-up of FUO when diagnostic clues are absent. FDG-PET/CT appears to be a cost-effective routine imaging technique in FUO by avoiding unnecessary investigations and reducing the duration of hospitalization and should be performed when fever is present or within one week in case of elevated CRP.

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Table 1. Review of the literature on FDG-PET/CT in patients with FUO

Reference	Study design (no. of patients)	FUO definition	Helpfulness FDG-PET/CT
Keidar 2008 [24]	Prospective (48)	Fever > 38.3°C > 3 wk; no diagnosis after 1 wk of in-patient investigations	46%
Balink 2009 [25]	Retrospective (68)	Not specified	56%
Federici 2010 [26]	Retrospective (10)	Fever > 38.3°C > 3 wk; no diagnosis after 1 wk of in-patient investigations	50%
Ferda 2010 [27]	Retrospective (48)	Not specified	54%
Kei 2010 [28]	Retrospective (12)	Fever > 38.3°C > 3 wk; no diagnosis after > 3 d in-patient investigations or 2 wk out-patient investigations	42%
Sheng 2011 [29]	Retrospective (48)	Not specified	67%
Pelosi 2011 [30]	Retrospective (24)	Not specified	46%
Pedersen 2012 [31]	Retrospective (22)	Fever > 38.3°C > 3 wk; no diagnosis after 3 d of in-patient investigations	45%
Crouzet 2012 [32]	Retrospective (79)	Not specified	75%
Kim 2012 [33]	Retrospective (48)	Not specified	52%
Manohar 2013 [38]	Retrospective (103)	Fever > 38.3°C > 3 wk; no diagnosis after > 1 wk of in-patient or out-patient investigations	60%

Tokmak 2014 [34]	Retrospective (21)	Fever > 38.3°C > 3 wk; no diagnosis after > 1 wk of in-patient investigations	60%
Buch-Olsen 2014 [39]	Retrospective (57)	Not specified	53%
Singh 2015 [35]	Retrospective (47)	Fever > 38.3°C > 3 wk; no diagnosis after > 1 wk of in-patient investigations	38%
Gafter-Gvili 2015 [37]	Retrospective (112)	Fever > 38.3°C > 3 wk; no diagnosis after > 1 wk of in-patient or out-patient investigations	46%
Pereira 2016 [36]	Retrospective (76)	Fever > 38.3°C > 3 wk	60%
Hung 2017 [40]	Retrospective (58)	Fever > 38.3°C > 3 wk; no diagnosis after > 1 wk of in-patient investigations	57%

Figures

Figure 1.

A 60-year-old woman presented with fever, night sweats, and arthralgia. Physical examination was normal. ESR was 125 mm/hour and leukocyte count was 12.4 x 10^9/l with normal creatinine level and liver function tests. FDG-PET/CT showed highly increased FDG uptake of the aorta, subclavian arteries, and femoral arteries. She was diagnosed with large vessel vasculitis. Her symptoms resolved and ESR normalized upon treatment with corticosteroids.

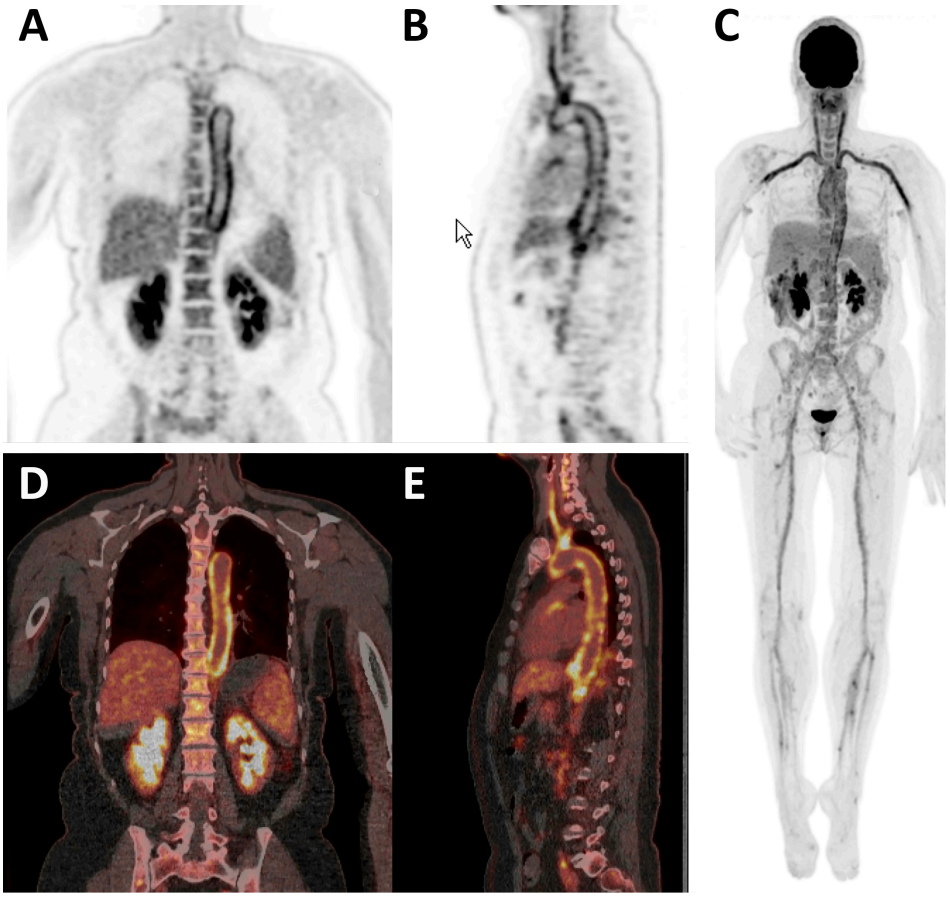

Figure 2.

A 75-year-old man, with a medical history of an aortic vascular prosthesis due to a symptomatic aneurysm and metastatic prostate carcinoma, presented with fever and night sweats. Physical examination was normal. CRP was 130 mg/L and leukocyte count was 11.0 x 10^9/l with normal creatinine level but increased AF (220 U/L) and LDH (771 U/L). FDG-PET/CT showed besides the known metastatic prostate carcinoma infection of the aortic graft. Blood cultures were positive for *Streptococcus anginosus* and the patient was treated with amoxicillin/clavulanic acid until his death 6 months later.