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Role of ^{18}F-FDG PET/CT in Renal Cyst Infection

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Abstract
Purpose of Review Cyst infection (CI) is a severe complication of cystic renal disorders, notably in autosomal-dominant polycystic kidney disease (ADPKD), and constitutes a diagnostic challenge because of the lack of specific clinical manifestations and limitations of conventional imaging methods. The role of ^{18}fluorodeoxyglucose positron-emission computed tomography combined with computed tomography (^{18}F-FDG PET/CT) in renal CI is reviewed.
Recent Findings Recent reports suggest that ^{18}F-FDG PET/CT is the best tool for CI detection. This technique has been demonstrated to play a role not only in the identification of CI, but also in the guidance of invasive procedures, in the detection of other infectious or even incidental neoplastic foci, and in monitoring therapy response.
Summary This article aims to review the role of ^{18}F-FDG PET/CT in renal CI, particularly in the context of ADPKD, compare this technique with conventional radiological and nuclear medicine methods, and discuss future perspectives in the approach to such a diagnostic challenge.

Keywords Positron-emission tomography/computed tomography · Renal cyst infection · Autosomal-dominant polycystic kidney disease · Simple renal cyst · Complex renal cysts · ^{18}F-fluorodeoxyglucose

Introduction

Cyst infection (CI) is a severe complication in patients with cystic renal disorders, notably in the context of autosomal-dominant polycystic disease (ADPKD) [1•], and constitutes a diagnostic challenge because of the lack of specific clinical manifestations and limitations of conventional imaging methods [1•, 2•, 3, 4, 5•, 6•, 7–12]. Currently, the gold standard in diagnosing CI is a cyst aspirate with the presence of bacteria and/or neutrophils suggestive of infection [1•, 2•, 5•, 10, 13, 14]. However, in most cases, a cyst aspirate is not available due to non-identification of the infected cyst by conventional imaging methods, or the procedure is not feasible because the suspected infected cyst cannot be accessed percutaneously. Therefore, diagnostic criteria have been proposed using a combination of clinical, biochemical, and imaging findings to establish a 'probable' CI diagnosis.

In recent years, ^{18}fluorodeoxyglucose positron-emission computed tomography, combined with computed tomography (^{18}F-FDG PET/CT), has emerged as a promising imaging technique for the evaluation of CI, not only in the identification and location of infected cysts, but also playing a role in the guidance of diagnostic and therapeutic invasive procedures, in the detection of other infectious or even incidental neoplastic foci, and in the control of treatment efficacy [2•, 3, 4, 5•, 6•, 7, 8, 10, 12, 15–18].

This article aims to review the role of ^{18}F-FDG PET/CT in the management of renal CI, particularly in the context of ADPKD, compare this technique with conventional radiological and nuclear medicine methods, and discuss

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future perspectives in the approach to such a diagnostic challenge.

Renal Cystic Disease and Infection

Cysts are the most common space-occupying lesions of the kidney [19]. Renal cystic disease comprises a wide spectrum of hereditary, acquired, and developmental conditions [20, 21], and renal cysts may represent the sole manifestations, accompany extrarenal abnormalities, or be a part of a well-defined syndrome [21].

Autosomal-dominant polycystic kidney disease (ADPKD) is the most common genetically transmitted renal cystic disease, with an incidence of one to 2 per 1000 live births [21]. ADPKD may manifest at any age, but mostly during the fourth and fifth decades [21], and is the fourth most common cause for renal replacement therapy worldwide [22]. In addition to kidney manifestations, a variety of extrarenal abnormalities can also occur, which mainly encompass cysts in other organs, particularly in the liver (94% prevalence in 35- to 46-year-old subjects), and connective tissue abnormalities, such as mitral valve prolapse (25%) and intracranial aneurysms (8%) [23].

Renal CI is considered a severe complication as cyst infections frequently lead to hospitalization and often require invasive treatment [1•, 5•]. In a review of 119 published renal CI cases from 70 articles [1•], renal CI occurred mainly in the context of ADPKD, and it was diagnosed in 91% of probable and 68% of definite CI cases. The remaining definite cyst infections were diagnosed in patients with solitary renal cysts (29%) or multiple renal cysts, not being ADPKD (3%).

The incidence of CI in ADPKD has been calculated as 0.01 episode/patient/year, according to an 11-year retrospective monocentric study [5•]. In the chronic hemodialysis (HD) population, the prevalence of renal infection is significantly higher in ADPKD patients than in patients who started chronic HD at the same time and appears even more so in patients with a history of pyocyst before the initiation of HD [24]. Pathogens usually include enteric flora, *Escherichia coli* being the most common agent [2•].

When renal or hepatic CI is suspected, the precise identification of the pyocyst(s) is crucial to provide percutaneous or surgical drainage of infected cysts, especially if the antibiotic therapy has failed [2•, 7, 13].

Diagnostic Criteria in CI

A cyst aspirate containing bacteria and/or neutrophils is the current gold standard in diagnosing renal and hepatic CI [1•, 2•, 5•, 10, 13, 14]. However, this procedure is not always available or viable, so that CI diagnosis relies practically on a combination of clinical, biological, and radiological parameters.

Sallée et al. [5•] recommended following clinical criteria based on an 11-year retrospective series of pyocysts in patients with ADPKD for a "probable" diagnosis of CI. According to these authors, CI is a probable diagnosis in the concurrent manifestation of four conditions: fever (temperature > 38 °C > 3 days), abdominal tenderness in the kidney or liver area, increased C-reactive protein levels (CRP, > 5 mg/dL), and the absence of any significant intracystic hemorrhage on computed tomography (CT) or other causes of fever. Nonetheless, none of these four criteria are specific to CI. They do not allow precise location of the pyocyst and cannot rule out a secondary infection complicating a cyst hemorrhage [2•]. The importance of the accurate location of infected cysts lies in the fact that resistant infection sometimes occurs even when suitable antibiotics have been administered. Drainage of infected cysts is often needed to avoid a fatal outcome, and percutaneous or surgical drainage of infected cysts is recommended when fever persists despite 1–2 weeks of appropriate antimicrobial therapy [13]. Therefore, anatomical and functional imaging techniques may play a crucial role in the evaluation of CI in the context of ADPKD.

Radiological Findings

Imaging techniques could prove to be helpful tools in diagnosing CI, but studies indicate that conventional imaging is of limited use [1•, 2•, 3, 4, 6•, 7, 8, 10, 18]. Radiological findings usually associated with CI include the detection of debris with a thick wall and/or a distal acoustic enhancement in at least one cyst on ultrasound (US), and the detection of enhanced wall thickening and/or perilesional inflammation in at least one cyst on CT and magnetic resonance imaging (MRI) [5•]. Additional evidence of infection includes fluid–fluid level and detection of gas inside the cyst [13]. However, the presence of intracellular debris, hyperattenuating on CT, shows a poor specificity to differentiate infected from non-infected cysts in ADPKD patients. In addition, contrast enhancement lining cyst walls can be caused by either inflammation or residual parenchyma [2•].

In the series of Sallée et al. [5•], US, CT, and MRI failed to detect the infected cyst in 94, 82, and 60% of cases, respectively, and most importantly yielded negative results in more than half of patients with a definite diagnosis of cyst infections.

These results are similar to those found by Lantinga et al. [1•]. In a review of the available diagnostic criteria

concerning CI, with the characterization of 215 published CI cases from 70 articles, US and CT were negative in ~ 40% of scans performed in definite CI cases. Contrast-enhanced CT and MRI were diagnostic in up to 100% of scans [1•], but the experience with these techniques is limited. Moreover, the use of contrast agents in ADPKD patients with impaired renal function is relatively contraindicated [2•, 17]. Some authors indicate CT scan primarily to exclude intracystic hemorrhage [1•, 5•, 10, 13] and to rule out non-cystic diseases in the febrile abdomen in ADPKD patients [8, 25].

Recent technological advances have made diffusion-weighted imaging (DWI) a valuable MRI technique in renal and hepatic lesion evaluation [1•, 2•, 13, 26, 27]. DWI expresses the rate of water molecule diffusion between tissues, given as the apparent diffusion coefficient (ADC) [1•]. Some anecdotal cases of infected renal cysts with high signal intensity in diffusion-weighted MR imaging (DWI) have been described [12, 27]. A marked decrease in the ADC value is thought to indicate CI [1•, 2•, 13]. However, established ADC threshold values indicating CI are lacking, which currently limits its clinical applicability [1•]. Further prospective investigations are needed to evaluate this novel imaging tool [2•].

Conventional Nuclear Medicine Imaging

Scintigraphic techniques using tracers such as ^{67}gallium-citrate (^{67}Ga) and ^{111}indium-labeled leukocytes (^{111}In-labeled leukocytes) are available for imaging infection. Labeled leukocyte imaging is theoretically the radionuclide imaging technique of choice for detecting the majority of infections. Although these radiopharmaceuticals are routinely used in clinical practice, they have several disadvantages, such as normal accumulation in the liver and spleen, low image resolution, and high radiation burden (^{67}Ga). Furthermore, physiologic bowel uptake of ^{67}Ga is a known obstacle in the interpretation of ^{67}Ga scans [4].

Also, ^{67}Ga scintigraphy has been shown to have a sensitivity of 50% in detecting renal CI in ADPKD patients, suggesting that ^{67}Ga imaging is not very helpful in diagnosing cyst infections in these patients [17]. As ^{67}Ga scintigraphy, there are only few case reports on the successful use of ^{111}In-labeled leukocytes imaging in ADPKD. Moreover, the preparation of labeled leukocytes is laborious and can be hazardous because of handling of potentially contaminated blood [2•, 4, 17], and at least 24-h delay is required before imaging [2•] in both techniques. ^{111}In-labeled leukocytes scintigraphy is characterized by poor spatial resolution, low sensitivity, high radiation activity, and significant inter-observer variability [2•, 6•, 14]. Furthermore, the use of ^{111}In-labeled leukocytes scanning in febrile renal transplant patient raises concerns because of unspecific accumulation of white blood cells (WBC) in renal and pulmonary parenchyma [2•].

Hexamethylpropylene amine oxime (HMPAO) represents an alternative lipophilic chelator for efficient labeling of leucocytes with ^{99m}Technetium (^{99m}Tc). Radiation characteristics of ^{99m}Tc-HMPAO are more favorable for imaging than those of ^{111}In, particularly for single-photon emission computed tomography (SPECT). Furthermore, the dual modality technique combining CT with SPECT (SPECT/CT) using radiolabeled WBC has been associated with a diagnostic yield of 85% of cases with abdominal infections [28]. The relevance of SPECT/CT to CI diagnosis in ADPKD patients is currently unknown [2•].

^{18}F-FDG PET/CT in Imaging of Suspected Kidney and Liver CI

^{18}F-FDG PET/CT is a reliable tool for the detection of tissue infection, by the high metabolic activity and increased uptake of the glucose analog, ^{18}F-FDG, by inflammatory cells [2•, 29].

^{18}F-FDG is a non-physiological glucose analog, which undergoes metabolism by the same physiological processes as glucose, including being taken up by cell surface transporters (GLUT) and being transformed by the rate-limiting glycolytic enzyme, hexokinase, into ^{18}F-FDG-6-phosphate. Phosphorylated glucose enters the glycolytic pathway for energy production. Phosphorylated ^{18}F-FDG, however, is not further metabolized and remains trapped in the cells [30, 31].

Inflammatory cells, such as macrophages and granulocytes, demonstrate overexpression of GLUT transporters, mainly GLUT-1 and GLUT-3, and overproduction of glycolytic enzyme. This increased tissue glycolysis, as opposed to normal cells, and the consequent differential in the uptake of ^{18}F-FDG, form the pathophysiological basis of the use of ^{18}F-FDG PET/CT in infection and inflammation evaluation [12, 31].

Recent reports suggest that PET/CT is the best imaging tool for CI detection in ADPKD patients.

In a review of 215 published CI cases from 70 articles [1•], ^{18}F-FDG PET/CT was shown to detect 100% of definite and 93% of probable CI. US and CT were negative in ~ 40% of scans performed in definite CI cases. Contrast-enhanced CT and MRI were diagnostic in up to 100% of scans, but the experience with these techniques is limited. Moreover, the use of contrast agents in ADPKD patients with impaired renal function is relatively contraindicated [1•, 2•, 17], whereas ^{18}F-FDG is not nephro- or hepatotoxic and has been successfully used in patients with renal

function ranging from mildly reduced glomerular filtration rate (GFR) to end-stage renal disease [2•].

These findings are in agreement with those of other authors. Jouret et al. [10] showed a sensitivity of 84.6% for ^{18}F-FDG PET– CT, which was superior to that of CT. Sallée et al. [5•] showed a sensitivity of ^{18}F-FDG PET–CT of 100%, which was also superior to those of CT and MRI. Balbo et al. [3] reported sensitivities of 25, 71.4, and 95% for CT, MRI, and ^{18}F-FDG PET– CT, respectively.

The advantages of ^{18}F-FDG PET/CT in infectious diseases compared to conventional nuclear medicine techniques include: early imaging (often acquired from 1 h after radiotracer injection), resulting in early reporting; no need for in vitro cell labeling; high target-to-background ratio; high inter-observer agreement; and high-resolution tomographic images [2•, 30].

^{18}F-FDG PET/CT may be helpful in differentiating renal from hepatic CI in ADPKD patients [32], and in guiding percutaneous management in patients who are unresponsive to first-line antibiotics [16, 32]. This hybrid imaging technique also offers the additional advantage of whole-body screening, thereby occasionally identifying non-cystic inflammatory disorders and incidental neoplastic findings [2•, 3]. Furthermore, follow-up ^{18}F-FDG PET/CT is potentially useful in tailoring antibiotic treatment by evaluating individual treatment response [1•, 3, 6•, 11].

The most commonly described image pattern for CI in ^{18}F-FDG PET/CT is a focally increased uptake of the radiotracer lining at least one cyst (Figs. 1, 2, 3), in strong contrast with the physiologic accumulation in the parenchyma and distant from the pelvicalyceal physiologic excretion [10]. Another imaging pattern, described by Balbo et al. [3], is characterized by diffuse ^{18}F-FDG accumulation within the cyst (Fig. 1), which was demonstrated in 60% of all episodes in their series. Measurement of the maximum-standardized uptake value (SUVmax) has also been shown to contribute to CI diagnosis, with values > 5.0 highly suggestive of infection [3].

CI was demonstrated to be predominantly multifocal in both kidney and liver (Figs. 1, 2, 3), with the dominant cyst being infected in only 29.2% of CI episodes, indicating that a search focused on it can often be misleading. Kidney CI was also associated with higher total kidney volume (TKV) and height-adjusted TKV, suggesting kidney volume as a risk factor for kidney CI [3].

The injected activity of ^{18}F-FDG described in Europe is in the range of 2.5–5.0 MBq/kg, that is, 175–350 MBq or 4.7–9.5 mCi in a 70-kg standard adult, although the required dose may depend on the imaging device and the acquisition time used, whereas the reported ^{18}F-FDG administered activity in the United States varies from 370 to 740 MBq (10–20 mCi) for adults and 3.7–5.2 MBq/kg (0.10–0.14 mCi/kg) for children [33]. Patients must fast for at least 4–6 h before ^{18}F-FDG injection. Blood glucose level must be measured before administering ^{18}F-FDG. Most institutions reschedule the patient if the blood glucose level is greater than 150–200 mg/dL. Reducing the serum glucose level by administering insulin can be considered, but the administration of ^{18}F-FDG should be delayed after insulin administration, depending on the type and route of administration of insulin [34, 35].

Images are carried out 60–90 min after ^{18}F-FDG injection. Delayed images, when necessary, may be obtained 3 h after furosemide administration, except when contraindicated, as in anuric patients. This approach can improve the contrast between kidney background and the high ^{18}F-FDG uptake by the infected cyst, facilitating diagnosis [3].

Repeating ^{18}F-FDG PET/CT after CI diagnosis may improve management in some situations, such as to confirm cure in patients with CI when surgical drainage was indicated, but not feasible or not performed due to technical difficulties, or when documentation of cure is necessary for other reasons, such as to initiate chemotherapy or to undergo a surgical procedure (Figs. 3, 4). The negative predictive value of ^{18}F-FDG PET/CT to exclude CI, however, needs to be assessed in future studies [3].

Disadvantages of ^{18}F-FDG PET/CT include high costs and limited availability. Furthermore, false-negative results in CI evaluation may be favored by the delay between initiation of antibiotic treatment and ^{18}F-FDG PET/CT [3, 11]. Shortening the delay to ^{18}F-FDG PET/CT to 7 days for all patients could improve the sensitivity of ^{18}F-FDG PET/CT in this setting [11].

Additionally, ^{18}F-FDG PET/CT has not been evaluated in intracystic bleeding, the main differential diagnosis of cyst infections in patients with ADPKD. Moreover, increased ^{18}F-FDG uptake has been reported in the setting of hematoma occurring in various extrarenal sites. Thus, the specificity of ^{18}F-FDG PET/CT for CI remains to be assessed. Nonetheless, significant intracystic bleeding is easily detected on CT scan. Hence, significant intracystic bleeding usually had been ruled out by CT scan in ADPKD patients undergoing ^{18}F-FDG PET scan for suspected CI [2•, 5•].

Ultimately, ^{18}F-FDG uptake may vary upon its diffusion into the lesion, the size of the lesion and the degree of respiratory mobility of the organ under investigation [2•, 34]. Each of these conditions may be responsible for "false-negative" ^{18}F-FDG PET/CT scans. Therefore, the correlation with clinical data and other imaging modalities findings is essential for the optimization of the interpretation of ^{18}F-FDG PET/CT images in the clinical context of suspected CI [10]. Further studies are required to more accurately determine its sensitivity and specificity, and to evaluate its role in assessing therapy response.

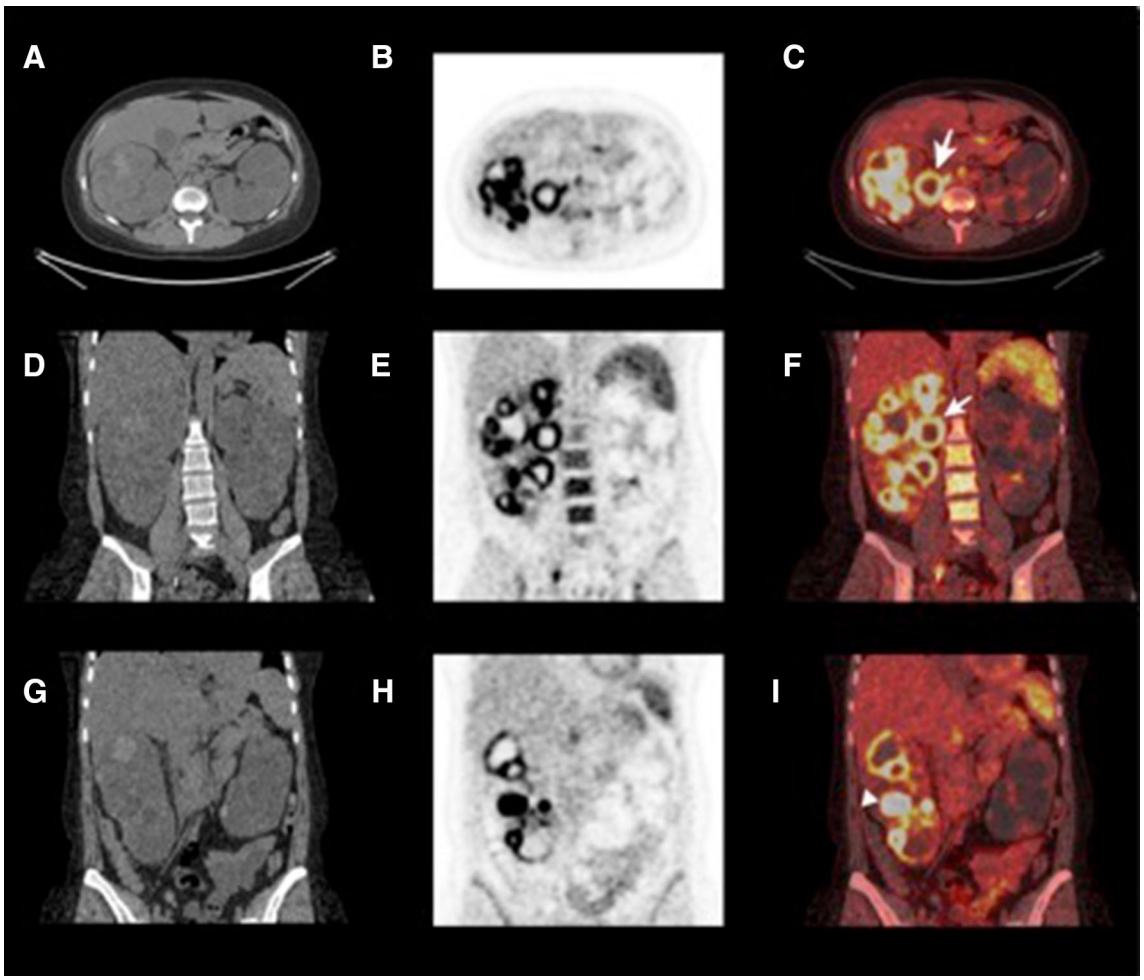

Fig. 1 CI in a 34-year-old female ADPKD patient documented by ^{18}F-FDG PET/CT. Axial (**a–c**) and coronal (**d–i**) CT, PET, and fused PET/CT images revealing two patterns of radiotracer uptake in the right kidney: increased cyst-lining 18F-FDG activity (arrows), and diffuse 18F-FDG accumulation within the cysts (arrowheads). The patient underwent right nephrectomy 15 days after ^{18}F-FDG PET/CT. Anatomopathological analysis confirmed acute infection, with abscess formation, and numerous fungal structures, compatible with *Candida spp*

Future Perspectives

Due to the interference of ^{18}F-FDG urinary excretion in the interpretation of renal lesions uptake [36], and due to the fact that WBC scintigraphy is considered the gold standard radionuclide imaging technique for diagnosing infectious disease [37], there has been studies with PET/CT using WBC labeled with ^{18}F-FDG for evaluation of CI in ADPKD patients [36, 37].

The distinction between ^{18}F-FDG-labeled WBC PET/CT and ^{18}F-FDG PET/CT is the type of cells detected by these tracers in infected sites. When WBCs are tagged by ^{18}F-FDG as a radiotracer, they reveal active diapedesis through chemotactic processes. Thus, ^{18}F-FDG-labeled WBC PET/CT may be a useful technique for finding focal inflammatory lesions, more specific than ^{18}F-FDG PET/CT [38].

Kim et al. [36] conducted a prospective case series in which 19 ADPKD patients suspected of having CI were enrolled to undergo ^{18}F-FDG-labeled WBC PET/CT. This technique accurately detected CI in 64%, had false-positive results in 2 of 5 cases with no CI, and 4 cases of false-negative. The two cases of false-positive results in Kim et al. study may be due to WBC leak from cyst cavities [36]. The authors recognize that some pitfalls occur because WBC accumulation requires an adequate host immune response to the CI. Glucocorticoids reduce the ability of leukocytes to adhere to vascular endothelium and to exit from the circulation leading to neutrophilia, so their entry into sites of infection and tissue injury is impaired, resulting in suppression of the inflammatory response, which is also observed with other immune suppressants like tacrolimus, used in kidney transplanted patients [39]. Therefore, in the immune suppressed state due to

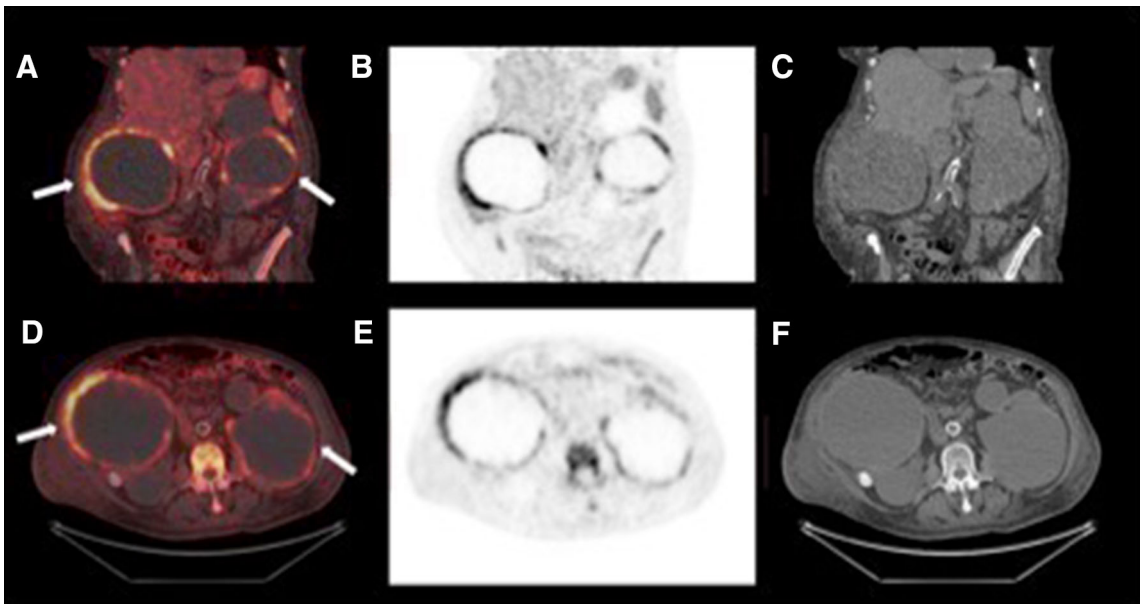

Fig. 2 Bilateral renal CI in an 80-year-old female ADPKD patient documented by ^{18}F-FDG PET/CT. Coronal (**a**–**c**) and axial (**d**–**f**) fused PET/CT, PET, and CT images revealing increased ^{18}F-FDG uptake lining cysts bilaterally (arrows)

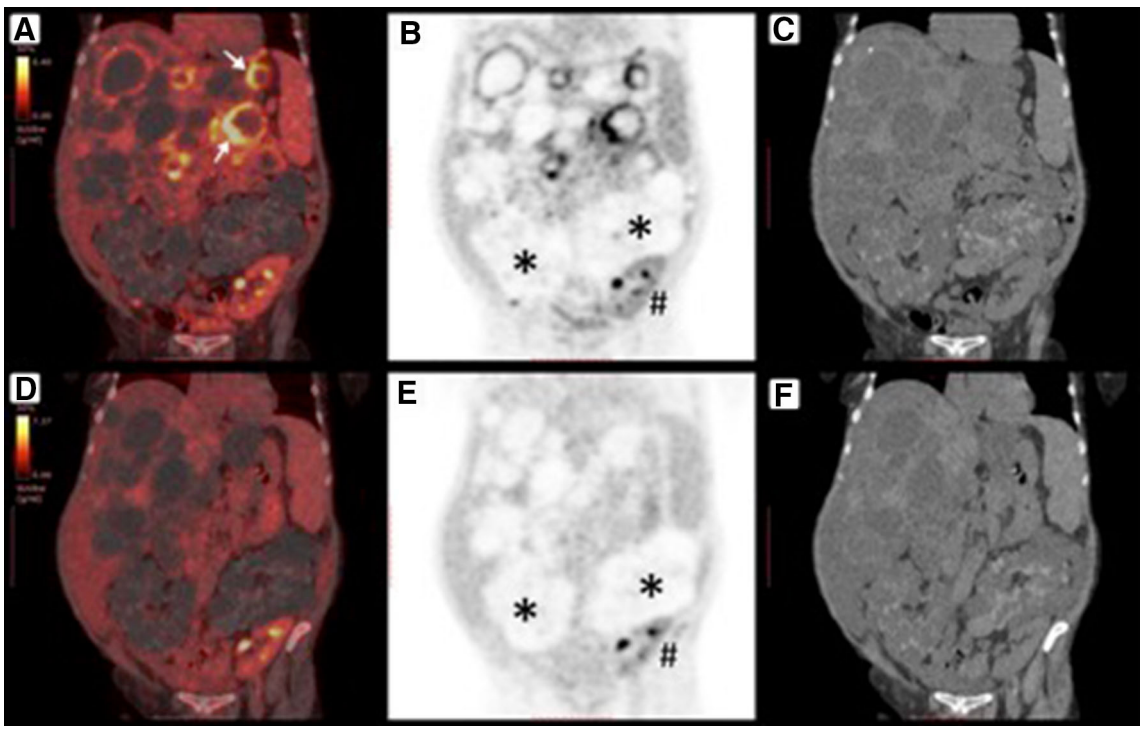

Fig. 3 Multiple infected liver cysts in a 59-year-old female ADPKD patient documented by ^{18}F-FDG PET/CT. Coronal fused PET/CT (**a**), PET (**b**), and CT (**c**) images revealing increased ^{18}F-FDG uptake lining multiple liver cysts (arrows). There is no abnormal ^{18}F-FDG in renal cysts (asterisks). Physiological uptake and excretion of ^{18}F-FDG are observed in kidney graft (pound signs).^{18}F-FDG PET/CT after treatment (**d**, **e**, **f**) demonstrating complete disappearance of abnormal ^{18}F-FDG accumulation

immunosuppressant drugs, WBC PET/CT can show false-negative results [36].

Kwon et al. studied 17 patients with ADPKD and suspected CI, classified as having definite/probable/possible CI. The diagnostic performance of WBC PET/CT demonstrated a sensitivity of 85.7%, specificity of 87.5%, positive predictive value of 85.7%, and negative predictive value of 87.5% [37].

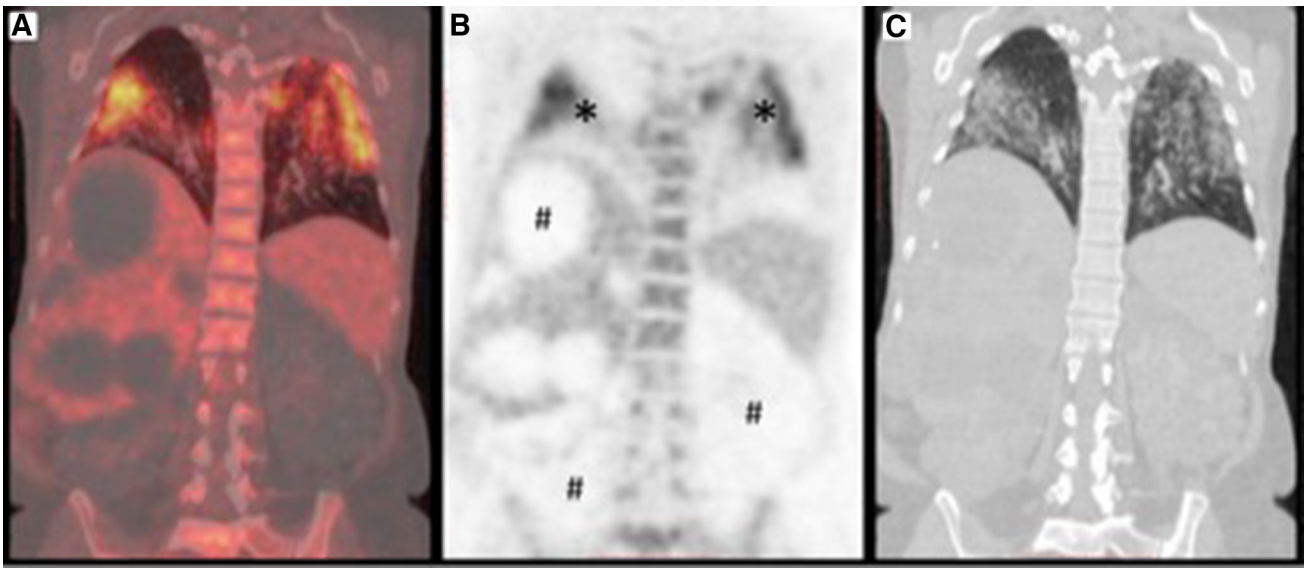

Fig. 4 Same patient as in Fig. 3. Coronal fused PET/CT (**a**), PET (**b**), and CT (**c**) images (lung window) revealing ^{18}F-FDG uptake in bilateral pulmonary opacities (asterisks), suggestive of lung inflammatory/infectious process. There is no abnormal ^{18}F-FDG accumulation in liver or renal cysts (pound signs)

These studies demonstrated that WBC PET/CT is another option for investigation of infected cyst in patients with ADPKD. However, the preparation of labeled leukocytes can be hazardous because of handling of potentially contaminated blood. Furthermore, the costs are high and more studies comparing ^{18}F-FDG PET/CT and ^{18}F-FDG-labeled WBC PET/CT in CI in ADPKD patients are needed to prove the superiority of ^{18}FDG-labeled WBC PET/CT.

PET/MRI

The integration of PET and CT technology into PET/CT inaugurated a new era of hybrid imaging, and the information value exceeds the sum of its parts. Inspired by this success, efforts were made to the development of PET/MRI system. Due to limited availability of PET/MRI system, this type of modality of hybrid imaging cannot be regarded as an established modality for clinical practice, but it is a promising technology, with clinical and scientific value yet to be defined [40]. There are many studies with specific focus on applications of this modality. In the context of infected cyst in ADPKD patients, it is interesting to sum the information of ^{18}F-FDG PET/CT images to MRI technology, including MRI specific tools as diffusion-weighted imaging (DWI). However, further prospective investigations are needed to evaluate this novel hybrid imaging technology.

Conclusions

Renal CI is considered a severe complication that frequently leads to hospitalization, and often requires invasive treatment. The diagnosis and localization of renal CI are crucial to decide treatment strategy. Recent reports suggest that ^{18}F-FDG PET/CT is the best tool for this purpose and this technique has also been demonstrated to play a role in the detection of other infectious sites, such as infected liver cysts, or even in the detection of incidental neoplastic foci, and in monitoring response to therapy. ^{18}F-FDG is not nephro- or hepatotoxic and has been successfully used in patients with renal function ranging from mildly reduced GFR to end-stage renal disease. Further studies are required to more accurately determine its sensitivity and specificity, and to evaluate its role in assessing therapy response.

Compliance with Ethical Standards

Conflict of interest Cristina Emiko Ueda and Carla Rachel Ono each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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