A new potentially promising concept in diagnosis of occult infection with help of PET-CT

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ABSTRACT

In the light of recent advances in radionuclide diagnostics of occult infectious states, it is clearly seen that positron emission tomography will have a part in routine work-up especially for critically ill patients in near future. For the purpose of further development of a specific agent that might be capable of detecting a living microorganism in occult focus inside the host organism, we come with a concept of probably a new radiopharmaceutical agent besides well-known fluorinated glucose, labeled leucocytes and gallium based radiopharmaceuticals. The aim of this opinion letter is to propose a specific agent for almost all bacteria and fungi genera not depending on host’s metabolism, thus letting differentiation of infection foci from host’s tissue. The discussion of this letter is mainly on the background of developing a compound for folate biosynthesis in bacteria and fungi which is a specific way of metabolization by the mentioned species which is provided by microbiological studies.

Key words: Diagnosis of occult infection; fever of unknown origin; PET-CT in diagnosis of infectious complications; PET-CT in diagnosis of occult infection; radiopharmaceutical agents.

LETTER

Infectious complications represent a big challenging problem in modern therapeutic practice. In some situations, the clinician has to focus only on the diagnosis of any occult infection to at least empirically start treatment. Indeed, in real practice there are many situations, especially in critical care when a practitioner faces a challenge expressed in patient having fever of unknown origin (Horowitz 2013; Lemmen & Lewalter 2012; Turkulov et al. 2011; Vertenoeil et al. 2012). Sometimes this problem originates from a region of infection which was not satisfactorily drained by surgical methods leading to ineffectiveness of wide spectrum antibiotics therapy.

Whole-body screening with functional imaging to detect some virtual missed infection in a patient is a well-known practice. There has been a tendency aiming not to specify the agent responsible for some clinical observation but at least find a focus of probable infection. As a brief summary, $^{67}$Ga scan and labeled leukocyte imaging have been commonly used for this purpose. Labeled leukocyte scan is usually preferred in patients with suspected infection. $^{67}$Ga scan has the ability to image both infection/inflammation and malignant processes; so it is preferable in patients who has the possibility of having tumor, autoimmune disease or infection (Kostakoglu et al. 2002; Mansberg et al. 2001; Nishiyama et al. 2002; Tsai et al. 2001). However, $^{67}$Ga scan has relative disadvantages; such as long imaging time for the patient, low resolution - low contrast affecting the image quality and difficulty in the evaluation of the...
abdominal region because of the physiological distribution of the radioactive agent. Three/four-phase bone scintigraphy which has good sensitivity but lower specificity, sequential bone\textsuperscript{67}Ga scan with increased specificity, and labeled leukocyte imaging have all been used for the detection of musculoskeletal infection. \textsuperscript{67}Ga scan is preferable for spinal osteomyelitis (Kumar & Boddeti 2013; Love et al. 2000; Mansberg et al. 2001).

The idea to evaluate the power of Positron Emission Tomography (PET) in screening infectious complications and nosologies is being actively investigated (Balink & Reijnen 2007; Balink et al. 2012; Bleeker-Rovers et al. 2004; Datz & Morton 1991; Lee & Redmond 2012; Love et al. 2005; Manohar et al. 2013; Servaes 2011; Shim et al. 2012; van der Bruggen et al. 2010; Vos et al. 2006; Zhou & Better 2004). \textsuperscript{18}F-fluorodeoxyglucose (FDG) has high concentration in inflammatory cells (neutrophils activated macrophages) and malignant tissue due to the increased glucose utilization and overexpression of glucose transporters of these types of cells. FDG-PET has better resolution/ image quality and short imaging time. FDG-PET has been shown to be useful diagnostic tool in fever of unknown origin, osteomyelitis, painful prostheses, sarcoidosis, acquired immunodeficiency syndrome, active vasculitis.

Recently, many teams have tried to find some specific radiopharmaceutical agents to interpret infection (Kumar & Boddeti 2013; Palestro & Love 2007; Rini & Palestro 2006). Such preliminary reports suggest that \textsuperscript{68}Ga-Citrate PET-CT is useful in the diagnosis of suspected bone infections and \textsuperscript{68}Ga-Transferrin PET-CT could be capable of detecting both Gram-positive Staphylococcus aureus (Staph A) and Gram-negative Proteus mirabilis. FDG-labeled leukocytes seem to be a promising, infection-specific positron emitting tracer. Also, these functional-imaging studies have the advantage of higher imaging characteristics of PET-CT.

So, in current status, most of the studies have been focused on studying the effect of infection on human rather than studying the effect of human on microbiome (Kumar V Fau - Boddeti et al. 2011).

In late November of 2012 sitting and listening to the long lasting discussion on the subject of infected necrotizing acute pancreatitis (2012 Istanbul – Congress of the European Surgical Society held in Turkey) we realized that the discussion was not about finding out some specific bacterial agent inside the cavity of assumed necrosis, but about the way of diagnosing the presence of infection in general without any specification. On the basis of fundamental of bacteriologic studies, in most cases pancreatic necrosis is typically infected by Pseudomonas, Escherichia coli, Klebsiella, Proteus, Enterobacter, and Staphylococcus species (Mary E. Klingensmith 2011). So, the point was to find out if there was actually any active infection or
not. We thought that it would be possible to diagnose bacterial and fungal infection with help of some common metabolic way specific for these genera.

Further investigations using free bioinformatics resources (http://www.expasy.org/) led us to assess the information on common metabolic pathway for all plants, bacteria and fungi. All bacteria have ways for synthesis of tetrahydrofolate in presence of para-aminobenzoic acid (PABA) (Rossi et al. 2011; Wegkamp et al. 2007). PABA is a precursor agent in the bacterial synthesis of folate. Although, humans lack the enzymes to convert PABA to folate, some intestinal bacteria such as Escherichia coli can produce folate from PABA. The above spoken bioinformatics resource and literature (Levin et al. 2004; Wegkamp et al. 2007) provided empiric evidence of wide presence of this specific metabolic pathway among bacteria and some fungi species. Further investigation led us to understanding that some new concepts and approaches have to be developed in close collaboration with all adjacent fields, in our case it is microbiology, nuclear medicine and actually all clinical areas.

Balink et al in their study address right the same aim – to assess the FDG PET-CT in detection of fever or infection of unknown origin. They say that being highly sensitive FDG based evaluation lacks specificity to distinguish between infection, tumor or inflammation. So, according to spoken review Balink et al propose FDG PET-CT as an ideal first step modality in some routine investigation protocol (Balink et al. 2012).

Thereafter, pushing off the spoken resources and study by Balink et al we tried to delineate the problem of detecting living microbiome inside host and, by the way, see if such concept can be virtually applicable to some other areas, like microbiological and ecological research.

So, we came to a hypothesis: we propose a method for detection of any bacterial and possibly most fungal infections based on selective metabolization of radioactively labeled PABA by bacteria and fungi using technological basis of PET-CT imaging. Due to the impossibility of PABA metabolization by human, it would be a perfect way to provide a specific point of application for PET-CT in this context. Moreover, potential physiological distribution of such an imaging agent in intestinal region due to the mucosal microbiome could be topographically excluded from three-dimensional reconstructions after some technical studies.

Potential benefits of this kind of specific-metabolic diagnosis of infection agents/regions could be listed as the following:

1. Non-invasive diagnosis of foci thought to be infected by typical flora is important. One example for this type of focus could be pancreatic necrosis causing fever and other systemic
effects. Differentiation of necrosis from abscess is obligatory for the prescription of empirical antibiotic treatment. Another example is clinical situations related to resorptive fever in cases of hematomas and tumors undergone necrosis which are usually misdiagnosed as infected because of the impossibility of non-invasive differentiation of these two situations clinically, further resulting in unnecessary prescription of antibiotics. On the other hand, medical treatment should be separate for any kind of occult infection such as infective endocarditis, chronic infections of gynecologic and abdominal origin, infections of implanted prostheses and catheters, infiltrating infections of soft tissues and abscesses of different localizations and so on.

2. Cost-effectiveness both in the diagnostic procedure and, which is far more important, relevant use of empirically prescribed antibiotics is anticipated according to our preliminary calculations.

3. A whole new research tool for detection of normally non-cultivated species inhabiting human body and environment (possibly Archaeae). With further development of more specific agents targeting folate biosynthesis pathway there should be found some new way to study the role of Archaeae in microbiome and biosphere composition as well.

A pilot study with further development of full experimental study is being designed by our team at the time.

REFERENCES


