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EDITORIAL

PET/CT IMAGING IN AUTOIMMUNE DISORDERS

Update on PET/CT in autoimmune disorders

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Inflammation is involved in a wide variety of disorders including malignancy, infection and auto-immune diseases, and imaging-based inflammation is nowadays frequently used for timely diagnosis and monitoring of treatment response. Following the clinical introduction of stand-alone positron emission tomography (PET) using 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) in the 1970's with the initial intent to explore applications in the central nervous system, and after technological advances in detector material making whole-body scanning possible, the first applications of [^{18}F]FDG/PET for imaging tumors and inflammation arose in the mid-1990s.[1] With the introduction of hybrid PET/CT cameras, that significantly improved anatomical localization, and their widespread availability from 2001 onwards, the application of PET/CT for inflammatory/infectious diseases has rapidly increased. While various radiotracers exist for imaging inflammation, [^{18}F]FDG is the most commonly used PET tracer. The main mechanism of [^{18}F]FDG uptake in inflammation is similar to that of malignant tumors, because cells involved in inflammation, especially neutrophils and the monocyte/macrophage lineage, are characterized by an increased glucose metabolism due to high expression levels of glucose transporters and hexokinase activity.[2, 3] In 2013, the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) published a guideline for [^{18}F]FDG use in inflammation and infection with sarcoidosis and large vessel vasculitis (LVV) being the two major indications based on the available evidence at that time.[4] In the last decade, the use of [^{18}F]FDG PET/CT imaging in inflammation has rapidly evolved and is nowadays the most commonly used nuclear medicine imaging technique to diagnose and manage several inflammatory disorders.[5] Autoimmune disorders are basically inflammatory conditions arising from an abnormal immune response that can affect a wide range of organs and tissues. To prevent irreversible tissue damage and sometimes severe clinical consequences, autoimmune disorders need to be promptly diagnosed and treated, and highly sensitive imaging techniques such as PET/CT may play a valuable role in this setting. This special monographic issue of the *Quarterly Journal of Nuclear Medicine and Molecular Imaging* focuses on the existing evidence of PET/CT in autoimmune disorders with an emphasis on the role of [^{18}F]FDG PET/CT for diagnosis, assessment of disease activity and therapy monitoring. Possible limitations and findings that should be adequately recognized and interpreted are also discussed. The 2013 EANM/SNMMI guideline already included LVV as one of the major indications for [^{18}F]FDG PET/CT and its use for the diagnosis of LVV is now well established according to the recent EULAR 2018 recommendations.[6] The role of [^{18}F]FDG PET/CT in patients with suspected LVV continues to expand from diagnosis to assessment of inflammatory disease burden and treatment response monitoring, as extensively shown by the review of Jamar *et al.*[7] Visual [^{18}F]FDG PET/CT analysis is still considered the standard for routine clinical practice but the use of (semi-)quantitative composite scores may have advantages to assess disease burden or response to treatment.

In contrast to LVV, strong evidence for PET/CT imaging is lacking for other autoimmune diseases that are currently not considered in guidelines but several studies point out that [18F]FDG PET/CT could play a valuable additional role in the diagnostic work-up of these disorders. The article by Guarneri *et al.*[8] summarizes the potential usefulness of [18F]FDG PET/CT in different stages of systemic sclerosis, Sjögren's Syndrome and systemic lupus erythematosus for detecting disease activity, assessing response to treatment as well as for excluding or detecting coexisting malignancies.

Another area of interest is the use of [18F]FDG PET/CT and/or PET/MRI in inflammatory bowel diseases (IBD). The article by Lovinfosse *et al.*[9] summarizes the overall good results of PET/CT or PET/MRI in the diagnosis and follow-up of IBD but their added value over techniques that do not involve ionizing radiation has not been demonstrated preventing their inclusion in clinical guidelines. The authors discuss the challenges that should be overcome to envision a more prominent role for [18F]FDG PET/CT in the management of IBD in the future.

The next contribution provides a comprehensive overview on the role of PET/CT in autoimmune thyroid disorders. Califaretti *et al.*[10] recognizes the non-primary role of [18F]FDG PET/CT in the diagnosis or management of autoimmune thyroid diseases but underlines the importance of correctly recognizing and interpreting incidental thyroid findings in both symptomatic and asymptomatic patients.

Paraneoplastic autoimmune disorders comprise a heterogeneous group of autoimmune diseases associated with malignancy. Evidence-based data support the use of [18F]FDG PET/CT in patients with suspected paraneoplastic autoimmune disorders for detecting an underlying malignancy as shown by the umbrella review of Muoio *et al.*[11] To date, it remains unclear whether [18F]FDG PET/CT should be part of the initial work-up in patients with suspected paraneoplastic disorders or if it should be reserved for patients with negative or inconclusive conventional imaging findings.

Rheumatic diseases encompass a wide variety of diseases affecting joints, bones, cartilage, tendons, ligaments and muscles. Rheumatoid arthritis (RA) is the most common disease, but many other diseases can affect the joints and mimic RA and appropriate diagnosis and early treatment are of utmost importance to limit joint damage and long-term disability. The review by Graham *et al.*[12] shows the potential role of [18F]FDG PET/CT in patients with RA, especially in those cases with an unexpected disease course in order to search for another potential diagnosis. The authors summarize possible alternative PET/CT applications using different (innovative) tracers in RA related to scoring cardiovascular risk factors as well as theranostic approaches.

Last but not least, the role of [18F]FDG PET/CT to assess immune related adverse events (irAEs) in patients receiving immune checkpoint inhibitors is shown by Sachpekidis *et al.*[13] In recent years, immunotherapies have represented a major advance in cancer therapy resulting in unprecedented response and survival rates, but these immunotherapeutic strategies exert their effect at the cost of irAEs. The review by Sachpekidis *et al.* describes the most common irAEs observed on [18F]FDG PET/CT as well as the association between signs of irAEs detected on [18F]FDG PET/CT and anti-tumor effect of immunotherapy.

Finally, more specific targeted radiotracers for a particular disease, are currently under development and investigated such as those targeting activated macrophages or the fibroblast activating protein. These biomarkers could prove useful for molecular characterization of inflammatory lesions, selection of candidates to immunotherapies, prediction of therapy response and follow-up. We hope to share our enthusiasm on the bright future of PET imaging in inflammation in general. We would like to thank all authors for their excellent contributions to this special issue. We hope that this issue will serve as a forum to raise awareness of the potential usefulness of PET/CT imaging in autoimmune disorders and that well-designed prospective multicenter studies with larger patient cohorts will be carried out to provide clear answers on the role of PET/CT in the clinical management across the wide spectrum of autoimmune disorders.

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