EDITORIAL

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Utility and drawbacks of [18]F-fluorodeoxyglucose positron emission tomography in the evaluation of adult-onset Still's disease

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Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology characterized by a high spiking fever, an evanescent salmon-colored maculopapular rash, arthritis, and neutrophilic leukocytosis [1]. Various systemic manifestations are known; serious complications may develop in some patients who require intensive immunomodulatory therapy. Approximately 60% to 70% of patients develop a chronic polycyclic form of disease or chronic polyarthritis, which eventually induces joint destruction [1]. The ability to reliably identify patients in which the disease is likely to progress allows for more active treatment of these patients via early prescription of biological agents.

Recently, several studies have shown that proinflammatory cytokines, including interleukin 1 (IL-1), IL-6, IL-18, tumor necrosis factor-α, and interferon-γ, are involved in the pathogenesis of AOSD [1]. The accumulated evidence indicates that the chronic form of AOSD can be divided into two distinct subtypes with different cytokine profiles: a predominantly systemic subtype and a predominantly arthritic subtype [1]. As our understanding of the roles played by cytokines in AOSD has advanced, anti-cytokine biologicals have shown promising results when used to treat some patients with refractory AOSD [1].

The diagnosis of AOSD requires exclusion of other febrile diseases, such as malignancy and infection, and other rheumatic diseases, including polyarthritis, systemic autoimmune diseases, and systemic vasculitis. AOSD lacks typical serological and pathological findings. Its diagnosis depends largely on the criteria suggested by Yamaguchi et al. [2], but specialists have not yet reached consensus in terms of the diagnostic criteria for AOSD. Inflammatory rheumatic disease must be diagnosed and treated early (preferentially preclinically) to prevent irreversible tissue damage. Thus, early diagnosis and targeted treatment require sensitive disease-monitoring techniques, including the use of disease-specific serological biomarkers and advanced imaging methods.

The use of informative biomarkers to modify the dosages of therapeutic regimens according to disease status is very important. Traditionally, the extent of AOSD activity has been measured using the criteria of Pouchot, based on 12 systemic clinical features: fever, the

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typical rash, sore throat, myalgia, arthritis, pneumonia, pleuritis, pericarditis, hepatomegaly or another liver abnormality, splenomegaly, lymphadenopathy, and leukocytosis (15,000 cells/mm^3) [3]. In addition, the serum levels of nonspecific acute-phase reactants, including C-reactive protein (CRP) and ferritin, and the erythrocyte sedimentation rate (ESR), are useful biomarkers in clinical practice [1]. To date, many biomarkers, including calprotectin, free IL-18, β2-microglobulin, vitamin B_{12}, high-mobility group B1, soluble CD163, S100A12, neutrophils (CD64+), CXCL-10(+)/CXCL-13(+) cells, and CD68(+)/H-ferritin(+) cells, have been evaluated to determine their ability to assess AOSD disease activity. However, their utilities in clinical practice have not been validated adequately. AOSD is rare, and the recruitment of sufficient numbers patients to impart adequate statistical power to clinical studies is difficult [4]. Additionally, such nonspecific inflammatory biomarkers may not accurately reflect disease activity in patients with AOSD, especially those under treatment with corticosteroids and/or immunomodulators. Some patients may exhibit high levels of inflammatory cytokines (for example, serum IL-18) even when they are in clinical remission, or may have silent disease with normal levels of CRP and ferritin, and a normal ESR [5]. During the clinically silent stage, the detection of residual disease activity using disease-specific biomarkers or specific imaging modalities assessing metabolic or immunological function is important. Such monitoring techniques would facilitate the care of patients with AOSD, minimizing flare-ups during the maintenance stage.

[18]F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) has been used to examine oncological patients; the technique exploits the increased aerobic glycolysis of cancer cells, which correlates with the expression level of hypoxia-inducible factor 1α (HIF1α). This factor regulates the expression levels of glucose transporters, hexokinase, and other factors, and shifts cancer cells into an oxygen-conservation mode; thus, increasing aerobic glycolysis [6]. FDG uptake is not limited to cancer cells, being exhibited also by various inflammatory cells, especially activated macrophages stimulated by cytokines under hypoxic conditions. Uptake by inflammatory cells requires HIF1α activation to permit tissue infiltration and cellular activation [7]. In vitro experiments and a few small clinical observational studies have shown that FDG uptake by inflammatory tissue seems to reflect inflammatory activity. Thus, FDG-PET/CT has been used to assess the status of various rheumatic diseases. The clinical utility of [18]F-FDG PET/CT for the examination of patients with active rheumatic diseases has been documented in those with rheumatoid arthritis, spondyloarthritis, polymyalgia rheumatica, relapsing polychondritis, immunoglobulin G4-related disease, large-vessel vasculitis, Wegener's granulomatosis, and inflammatory myositis [7].

Although [18]F-FDG PET/CT yields sensitive information on the inflammatory status of various sites, the tool is not disease specific. As AOSD is a systemic inflammatory disease exhibiting a variety of clinical manifestations, [18]F-FDG PET/CT may be useful in terms of evaluating the organs involved. Some case reports, small case series, and retrospective clinical studies have suggested that [18]F-FDG PET/CT is useful for the monitoring of disease activity in patients with AOSD [7-14]. FDG was accumulated principally in the bone marrow, spleen, lymph nodes, and joints. In addition, FDG uptake by the pericardium, pleura, salivary glands, eyelids, muscles, and major blood vessels, but not at the sites of the salmon-colored rash, has been reported [7,12,13]. Some researchers [8,9], but not others [7,12-14], have reported significant uptake in the liver. Theoretically, high-level liver uptake might reflect serious liver damage caused by activated macrophages [15]. Although such a diffuse uptake pattern is not specific to AOSD (being also evident in patients with other systemic diseases), such findings are very useful to exclude malignant disease and increase the accuracy of AOSD diagnosis when combined with certain clinical features. In addition, FDG uptake data can be used to identify appropriate biopsy sites, such as lymph nodes and bone marrow, especially in patients for whom conventional imaging methods yield negative results [13]. Therefore, when FDG PET/CT imaging is used appropriately, information that aids greatly in accurate diagnosis may be obtained, facilitating control of disease activity [13]. However, it must be kept in mind that PET/CT findings alone do not enable the differentiation of AOSD from malignant lymphoma [7,13].

Some studies have evaluated the utility of FDG PET/CT in the monitoring of disease activity and the re-

sponse to treatment [11,13]. Typical FDG PET/CT images from patients with AOSD show that FDG accumulation tends to decrease in the bone marrow, spleen, and lymph nodes after treatment; the maximum standardized uptake values (SUVs) fall. Such observations suggest that FDG PET/CT is useful for evaluation of the effects of treatment. Thus, FDG PET/CT has been suggested to be valuable in the long-term assessment of disease activity, but further studies are required to determine whether FDG PET/CT can be used to effectively identify patients who are likely to respond to treatment and have good long-term prognoses [11].

In this issue, An et al. [14] evaluate the clinical efficacy of 18F-FDG PET/CT in the assessment of disease activity in 13 Korean patients with AOSD. They evaluated PET/CT images visually and in terms of SUVs. They found that 90% of patients with active AOSD exhibited increased [18]F-FDG uptake by the lymph nodes, spleen, or bone marrow. Of 10 patients with active disease, 4 exhibited uptake at all three sites, but one patient with active disease was uptake negative. In general, the visual grades and SUVs of the lymph nodes, spleen, and bone marrow correlated significantly with the levels of known markers of disease activity. The authors suggest that [18]F-FDG PET/CT is useful for the evaluation of disease activity in patients with AOSD. However, the study was retrospective and cross sectional, thus lacking follow-up imaging to explore changes in disease activity with treatment. A future study should explore whether long-term prognosis can be predicted via initial and follow-up assessment of FDG uptake. Again, one patient with active disease was uptake negative, for unknown reasons. If such patients responded very well to treatment, thus exhibiting very favorable prognoses, such behavior would be very useful when seeking to predict long-term prognoses. The study included three patients lacking clinical activity who were uptake negative. These data, combined with the serum levels of inflammatory cytokines and therapeutic agents at the time of imaging, indicate that [18]F-FDG PET/CT may be useful to detect residual disease activity in patients with clinically silent, but serologically active, AOSD.

Together, the data indicate that [18]F-FDG PET/CT may allow early diagnosis (based on the typical uptake pattern) and guide the selection of biopsy sites in the management of patients with AOSD. FDG PET/CT may also aid the assessment and monitoring of disease activity during treatment, and the detection of residual disease activity in patients with clinically silent, but serologically active, disease. Further prospective clinical studies with larger numbers of patients are required.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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