EDITORIAL

Is There a Role for FDG PET Imaging in the Management of Patients with Sarcoidosis?

Sarcoidosis is a chronic inflammatory-granulomatous disease of unknown cause and can involve almost any organ. However, lungs are frequently affected and pulmonary manifestations of the disease dominate compared to other organs (*1,2*).

It is believed that the original pulmonary lesions consist of mononuclear (macrophage) cell infiltration of interstitial tissue of the lung. This inflammatory reaction is followed by formation of granulomas which are characteristic of this disease. While the majority of granulomas resolve over time, in some instances fibrosis ensues with subsequent tissue dysfunction (*3*). Therefore, disease activity can be best assessed by detecting and quantifying the inflammatory and granulomatous reactions that occur in the lungs and elsewhere in the body.

Clinical assessment of pulmonary involvement is considered important in the management of patients with sarcoidosis. Resting pulmonary function tests (PFTs) usually reveal a mixture of restrictive and obstructive patterns which are nonspecific findings (*4*). Chest x-rays are somewhat insensitive in detecting parenchymal involvement when compared to histopathological results. Up to 60% of patients with granulomata demonstrated on transbronchial biopsy are found to have normal chest-x-rays (*5*).

Conventional computed tomography (CT) can detect nodular and cystic lesions, adenopathy and pleural involvement. However, early and subtle abnormalities of the lungs are frequently missed by conventional CT techniques. The use of high-resolution CT (HRCT) may improve the overall accuracy in staging pulmonary involvement in sarcoidosis. In a recent retrospective study, Lynch et al. (*6*) reported very good sensitivity for HRCT in detecting pulmonary abnormalities in 15 patients with confirmed diagnosis of sarcoidosis. They also compared the results with those noted on ^{67}Ga scintigraphy. However, the extent of nodularity (considered as evidence for disease activity) seen on HRCT did not correlate with disease activity noted on the ^{67}Ga scan. Furthermore, in several cases the results of bronchoalveolar lavage (BAL) was considered as evidence for disease activity and not the histopathological examination. Also bias in selecting patients cannot be ruled out because of the retrospective nature of this study. It is well known that fibrosis of the parenchyma may persist during or after successful treatment which may result in inaccurate diagnosis (*7*).

MRI has also been utilized in the evaluation of patients with sarcoidosis. Muller et al. (*8*), who studied 25 patients with chronic infiltrative lung disease (6 of them secondary to sarcoidosis), showed MRI to be less accurate than HRCT in the anatomic assessment of lung disease. However, areas of air-space opacification (ground-glass opacities) were well visualized by MRI which correlated with the presence of alveolitis on histopathological analysis. Large scale prospective studies are necessary to establish the appropriate application of HRCT and MRI in staging and follow-up examination of patients with pulmonary sarcoidosis.

Functional imaging studies, such as those obtained with ^{67}Ga, have been used to diagnose and assess disease activity (*9–12*). The mechanism of ^{67}Ga-citrate uptake is unclear in many disorders in which this radiotracer is used for diagnostic purposes. However, it is believed that ^{67}Ga is actively taken up by mononuclear phagocytes in the lesions located either in the lungs or other organs in patients with active sarcoidosis (*13–15*). Measurable uptake of this agent is interpreted as evidence for active inflammatory disease (*16–18*). Quantitative measurement of ^{67}Ga uptake may allow assessment of the degree of the disease activity (*19*).

This scintigraphic study has been shown to be highly sensitive but somewhat nonspecific in this disorder. Some groups have suggested that with careful interpretation of "lambda" (peri, infra-hilar and mediastinal adenopathy) and "panda" (parotid and salivary glands involvement) patterns, the specificity of the test can be improved considerably. In a recent prospective study, Sulavik et al. (*20*) determined the sensitivity and specificity of these two patterns in 162 patients with sarcoidosis and in 167 HIV-positive patients (most of them with AIDS). The authors compared the scintigraphic results with those revealed by chest x-rays. Thirty-three percent of the patients with sarcoidosis and with normal chest x-rays showed evidence of active alveolitis by a ^{67}Ga scan. Also the lambda sign was not seen in any of the 167 HIV-positive patients, confirming the high specificity of this finding. The authors concluded that the high sensitivity and specificity obtained with the combined use of chest x-rays and ^{67}Ga scans preclude the use of invasive procedures for diagnostic purposes. The other advantage of ^{67}Ga is the potential for staging extra-thoracic involvement with a single injection and imaging session. Uptake of ^{67}Ga is noted in approximately two-thirds of patients with sarcoidosis and has been seen in over 90% of active cases (*21*). Negative ^{67}Ga scans have been reported in 68%–87% of cases with dormant disease.

Proponents of ^{67}Ga scanning in sar-

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coidosis believe that the findings on the images correlate with disease activity and is more sensitive than serum angiotensin-converting enzyme (ACE) level for following the course of the disease (*22*). However, controversies still exist regarding the use of bronchoalveolar lavage (BAL), ^{67}Ga and ACE level in the disease activity assessment of patients with sarcoidosis. A negative ^{67}Ga scan following adequate treatment is often associated with good response (*23*). However, a positive ^{67}Ga scan appears to provide little information with regard to response in these patients. In other words, a sizable number of patients with positive ^{67}Ga scans may not require therapy (*13,24*).

Evidence of increased glucose metabolism in inflamed tissue has been demonstrated by different experimental studies (*25–27*). In a longitudinal study, Daley et al. (*27*) demonstrated that increased glycolysis in injury-induced wounds is an aerobic process. They suggested that this increase in metabolic activity was related to the presence of inflammatory cells on sites of injury. Newsholme et al. (*28*) demonstrated that inflammatory cells produce 7–8 times higher levels of ATP in the activated states when compared to that in the baseline condition. Mauel (*29*) also showed significantly increased glucose oxidation through the hexose monophosphate shunt pathway when murine macrophages were exposed to dilutions of the bacterial extract OM-85 BV. The mechanisms underlying the high glycolitic rate in inflammatory tissue are not completely understood at the present time. Macrophages are known to have high rates of protein secretion and membrane recycling. Adequate concentrations of glucose-6-phosphate (for ribose phosphate formation) and glycerol-3-phosphate (for phospholipid synthesis), which are required as intermediate substrates for protein biosynthesis, are produced as a consequence of glycolysis. Therefore, rapidly dividing cells, such as activated inflammatory cells, have high glycolitic activity in order to satisfy their high energy demands. This is supported by the evidence of the increased metabolic activity noted during injury, trauma or sepsis which may be attributed to high demands for energy by macrophages and possibly other cells involved in the immunologic responses (*28*). Histologic studies of biopsy specimens suggest that macrophages, which contribute to granuloma formation, are activated (*30*). This may explain in part why granulomatous lesions show strong avidity for FDG.

The introduction of the ^{18}F-fluorodeoxyglucose (FDG) technique opened a new phase in the investigation of regional metabolic activities of various organs and many disorders. The FDG method is based on the biochemical properties of this chemical. FDG is transported between the blood and various tissues (this has been well established in the brain tissue) by the same carrier that transports glucose (*31*). FDG is phosphorilated by hexokinase to FDG-6-phosphate. However, in contrast to glucose-6-phosphate which is eventually metabolized to CO_2 and water, FDG-6-phosphate is not a substrate for glucose-6-phosphate dehydrogenase. Therefore, FDG-6-phosphate and its derivatives are essentially trapped in most tissues (including the tumor and inflammatory tissues) for at least a long enough time to allow imaging with modern PET instruments. Changes in tumor glucose transport and hexokinase activity will also affect transport and phosphorylation of deoxyglucose (*32*). Unlike the brain and heart tissues where the biochemical behavior of deoxyglucose is relatively well characterized, the exact mechanism of uptake and retention of this compound in the cancer and inflammatory cells remains to be explored. This lack of knowledge may prevent quantitative measurement of absolute metabolic rates in tumor and inflammatory tissues. However, semiquantitative techniques which have been validated and widely used, allow reproducible measurement of metabolic activities of the disorder.

The initial application of the FDG method in man included the investigation of the effects of various physiological and pathological states on regional brain metabolism and function (*33*). A great deal of knowledge has been gained about some complex disorders that affect the brain. Since the early 1980s, the potential applications of this technique in the investigation of coronary artery disease and cancer has been realized. The use of this methodology in the diagnosis, staging and follow-up of various malignancies has been quite rewarding and has overcome some of the deficiencies encountered with other imaging techniques (*34*). However, similar to other nuclear medicine and radiologic techniques, FDG uptake is not specifically seen in cancer tissues. As expected, it has been shown that sights of inflammation appear with high metabolic activity on FDG PET images. In experiments involving mice and rats, Yamada et al. (*35*) demonstrated similar accumulation of ^{67}Ga and FDG in inflammatory tissues. Meyer et al. (*36*) also showed intense accumulation of FDG in a 2-wk-old fracture of the clavicle and scapula, which probably represents reparative and inflammatory changes in the fractured site. Therefore, with this technique the potential for false-positive results exists when patients with cancer and coexisting inflammatory disorders are examined. However, in the appropriate setting, this undesirable behavior may provide useful clinical information. Detection of inflammatory sites in patients with suspected infection and determination of disease activity in an already diagnosed inflammatory disorder are of considerable clinical relevance.

In this issue of the *Journal*, Lewis et al. describe their preliminary results in two patients with proven sarcoidosis where the FDG PET images revealed intense uptake of the tracer in multiple sites corresponding to the involved structures (*37*). As the authors correctly point out, these cases clearly demonstrate the nonspecificity of the FDG PET technique in distinguishing an inflammatory process from that of malignancy. Since both sarcoidosis and lymphomas affect lymphoid systems throughout the body, the pattern noted on the FDG PET images is non-

specific and can not differentiate between the two. Therefore, the role of FDG PET imaging in the diagnosis of sarcoidosis is limited. However, in a patient with proven diagnosis of sarcoidosis, additional information may be obtained utilizing the FDG PET scan.

It is well established that PET generally provides high quality images with superior resolution and contrast compared to those acquired with SPECT. It is conceivable that the extent of involvement and quantification of the disease activity can be more accurately assessed by FDG PET than with ^{67}Ga scintigraphy and other imaging studies. Preliminary data provided by these authors support this. However, large-scale, well designed studies are necessary to define the role of this powerful technique in the management of patients with sarcoidosis. In the meantime, the routine use of PET in this disorder is unwarranted because of its limited availability and costs. Therefore, in spite of its deficiencies, ^{67}Ga scanning is considered the appropriate imaging study in the correct clinical setting in these patients. One must keep in mind that the use of high-resolution SPECT imaging to delineate the uptake of ^{67}Ga may improve its value in the assessment of patients with sarcoidosis. This may improve the ability to determine the extent and the activity of the disease. Finally, the introduction of new and novel tracers such as J001 macrophage targeting glycolipeptide (*38*) and ^{111}In-octreotide (*39*) may further improve our ability to diagnose, stage and monitor the course of the disease during and after therapeutic interventions.

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