EDITORIAL

Cancer or Inflammation? A Holy Grail for Nuclear Medicine

"Follow, follow, follow the gleam/of the chalice that is the Grail."
Sally Hume Douglas
[Follow the Gleam] Refrain, 1923

Nuclear medicine is continually seeking a tumor imaging agent that will provide the pathognomic sign to distinguish inflammation from tumor. 2-fluoro-2-deoxy-glucose (FDG) PET scanning has been proposed as a method of differentiating benign from malignant intra-thoracic lesions.

The current case report provides an important warning that we should proceed on this path with care (*1*). In their article Lewis and Salama report that FDG is not a cancer specific agent. Very impressive uptake of FDG was seen in two patients with sarcoidosis, both in the hilar lymph nodes and in associated extra-thoracic lesions of erythema nodosum. The authors conclude that "these cases provide evidence for the limited application of FDG PET to differentiate between lymphoma and sarcoidosis."

In pharmacological terms, FDG is one of the best characterized radiopharmaceuticals in use in nuclear medicine. The mechanism of increased uptake in tissues is based on accelerated glycolysis. Like glucose, FDG is transported into cells from the ECF on a glucose transporter protein which is insulin sensitive and rapidly converted into the FDG-6-phosphate, which is biochemically trapped in the metabolizing tissue. In tissues with active glucose-6-phosphatase, such as liver, the radiotracer can be cleared. However, in tissues such as brain and tumor which have an accelerated glycolysis, there is very little phosphatase activity, and the FDG-6P builds up in tissue over time in a manner dependent on the rate of glycolysis. This technique can be used to quantitate the metabolism of glucose utilization by tissue (*2*).

FDG PET imaging has a proven role in the assessment of some patients with cancer. With respect to primary brain tumors, FDG PET is the gold standard for differentiating recurrent tumor from radiation necrosis (*3*). Also, in the postoperative period, FDG PET is not taken up appreciably in brain tissue at the operative site. In a group of patients with lung tumor, FDG PET scanning was very useful for distinguishing benign solitary pulmonary nodules from malignant tumors (*4*). FDG PET scanning of the brain is useful in differentiating lymphoma (hot) from toxoplasmosis (cold) (*5*). Moreover, in virtually every tumor type studied with FDG, there is avid uptake of the tracer (Table 1). In fact, increased glycolysis is one of the most distinctive biochemical features of the malignant state (*6*), and the rate of increase correlates with growth rate (*7*). Perhaps this cluster of facts has led some to believe that we really could distinguish tumor from inflammation using FDG imaging.

Upon closer inspection of the literature, it is clear that strong FDG uptake has been seen in a variety of inflammatory lesions. In particular, the degree and type of inflammatory responses are important in determining uptake of FDG. Tuberculosis, fungal infections, cerebral abscess, have all been associated with FDG uptake. These infections are characterized by cellular infiltrates, granuloma formation and macrophage proliferation. Activated inflammatory cells have a markedly increased glycolysis and the hexose monophosphate shunt is stimulated by phagocytosis with increases of 20 to 30 times baseline being common in these stimulated cells (*8*). Even within tumors, the totality of FDG uptake is not completely within the tumor cells themselves. Indeed, about 24% of the FDG concentration in a tumor mass, is actually in macrophages, and other inflammatory cells within the tumor itself (*9*). Although tissue types may differ with regard to the absolute uptake of FDG, tumor uptake is usually greater than uptake in most types of inflammatory lesions (*6*). FDG uptake is more rapid in inflammatory cells (*10*), and avid FDG uptake is the rule in inflammatory tissue where the uptake is predominantly in the cellular component (Table 2).

The authors suggest that FDG PET scanning could be used to evaluate sarcoidosis extent and disease activity: "although this needs to be compared to the much cheaper and more readily available option of Gallium-67" (*1*).

Indeed, it is tempting to consider the possibility that FDG PET, where available, could substitute for ^{67}Ga whole-body scanning as an agent to assess disease activity and treatment response in a variety of disease states, including lymphoma, the immunosuppressed patient and sarcoidosis. For example, experimental studies (*E. Coli* induced and sterile abscesses in mice and rats) support the possibility that the time course of localization and lesion-to-muscle ratios are similar for FDG and gallium (*11*). Without considering expense, FDG PET scanning is likely to be favored by clinician and patient alike, because of same-day imaging and the inherent superiority of PET imaging methods over standard gamma camera imaging, in terms of sensitivity, resolution and the ability to assess the liver in late images after injection.

It is tempting but premature to make the leap equating FDG imaging with ^{67}Ga imaging in monitoring inflammatory states. In sarcoidosis, for example, what kind of information should be sought in comparative studies in order to develop enough evidence to justify replacing ^{67}Ga with

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TABLE 1
Neoplasms Concentrating FDG

Glioblastoma (*14*)
Meningioma (*15*)
Colon (*16*)
Breast (*17–19*)
Lung (*4*)
Hepatoma (*20*)
Sarcoma (*21*)
Head and neck tumor (*22*)
Ovarian (*23*)
Lymphoma (*24*)
Islet cell tumor (*25*)
Thyroid (*26*)

TABLE 2
Inflammatory Conditions Concentrating FDG

Sarcoid (*1*)
Tuberculosis (*4*)
Fungal infections (*4*)
Brain abscess (*27*)
Abdominal abscesses (*28*)
Pancreatitis (*25*)

FDG PET imaging? A brief review of the management issues involved in the sarcoid patient as they relate to nuclear medicine applications is in order.

Sarcoidosis is a chronic granulomatous disease of unknown cause with the potential for involvement of virtually every organ in the body and characterized by lymphadenopathy. Some sort of intra-thoracic involvement occurs in 90% of patients. Hilar or mediastinal adenopathy is common, and is often asymptomatic.

Gallium-67 is avidly taken up by active sarcoid disease, and the ^{67}Ga scan is frequently abnormal in particular patterns of uptake reflecting the common sites of disease activity, i.e., the "panda" pattern of salivary and lacrimal gland uptake was observed in 79% of sarcoid patients. Gallium-67 uptake in mediastinal and hilar lymph nodes forms a characteristic appearance on anterior planar images similar to the Greek letter lambda. This lambda pattern was observed in 72% of sarcoid patients (*12*).

Of particular clinical concern is the possibility of a progressive inflammatory lung syndrome which can result in severe chronic restrictive lung disease. In the early stages, there is a inflammatory cell infiltrate in the alveoli interstitium leading later to formation of interstitial noncaseating granuloma with an abundant cellular infiltrate. These inflammatory changes cause reversible symptoms, but may progress to fibrosis with a permanent loss of lung function.

Gallium-67 imaging is an excellent way to follow the activity of parenchymal lung disease since extent and magnitude of uptake correlate with disease activity both in terms of a correlation with ACE activity, and correlation with response to steroid therapy (*13,14*). Typically, the gallium scan shows perihilar uptakes which are bilateral, but any area of the lung can be involved. Other clinical benefits of ^{67}Ga scanning include identification of extrathoracic sites of disease as a guide to directed biopsy to obtain a definitive diagnosis (*15*).

The response of FDG PET imaging in mediastinal and hilar lymph nodes, extrathoracic sites of uptake in erythema nodosum and muscle, and the response of the uptake to steroid treatment in one patient, suggests parallels with ^{67}Ga-citrate as a way to monitor disease activity. Nonetheless, much work must be done to validate FDG PET so we can recommend this test with the same confidence as ^{67}Ga in sarcoid. FDG imaging has not been reported in a patient with active sarcoid pneumonitis, therefore, extensive comparison of FDG PET with ^{67}Ga citrate imaging in patients with active sarcoidosis involving lung should be performed in a serial fashion in treated patients. Correlation with other parameters of disease activity, such as angiotensin converting enzyme activity in plasma and pulmonary inflammation as assessed by pulmonary lavage, would also be essential to evaluate a potential role for FDG in assessment of disease activity in sarcoidosis.

This excellent case report describing the finding of FDG uptake in sarcoidosis can be thought of as a cautionary tale to help us put FDG into a more realistic clinical perspective. The biochemical process of glycolysis is reproducibly detected by this tracer. Glycolysis is accelerated in neoplasia, but it is not surprising that it is accelerated in other major disease processes as well, including the inflammation that occurs with sarcoidosis.

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