EDITORIAL
Benign Mediastinal and Parahilar Uptake of Gallium-67 in Treated Lymphoma: Do We Have All the Answers?

Galium-67 scintigraphy is now a clinically useful technique for the assessment of treated lymphoma due to newer cameras, SPECT techniques and the understanding that 67Ga is a viability agent. Although the sensitivity and specificity of 67Ga scintigraphy are reasonable, computed tomography (CT) and magnetic resonance imaging (MRI) are the usual techniques used for imaging patients with newly diagnosed lymphoma. On the other hand, 67Ga has been found to be a useful test in assessing response to treatment and predicting survival. Since there is effective treatment for lymphomas, 67Ga plays an important role in patient management, especially in patients who have residual mass after treatment (1,2).

Time and experience, however, have taught us that not every mass remaining after treatment of lymphoma is malignant nor that 67Ga uptake after treatment indicates viable tumor. The interpretation of 67Ga scintigraphy after treatment is not without problems. Nontumorous 67Ga uptake in the mediastinum in children and in adults is a problem for which a solution still has to be found. The use of SPECT enhances this mediastinal and parahilar uptake. Knowledge of normal and abnormal distribution of 67Ga does not always help in determining the nature of benign uptake.

In this issue of the Journal, Harris et al. (3) present a case of a 5-yr-old boy with Hodgkin’s disease, nodular sclerosis type, who demonstrated 67Ga uptake in what was apparently benign thymic hyperplasia after treatment. The mass, which was demonstrated by CT, took up 67Ga but was not considered to have taken 201Tl.

The patient did not receive further treatment, and follow-up showed that he was indeed in complete remission. Peylan-Ramu et al. (4) found that 67Ga uptake after treatment in patients with non-Hodgkin’s lymphoma had a frequency of 43% in children under 15 yr of age. The problem of rebound thymic hyperplasia (5–12), which takes up 67Ga, is apparently common and if the use of 201Tl will indeed differentiate between benign and malignant lesions after treatment, it will provide significant aid in determining treatment effectiveness.

Presently, thallium’s value in differentiating the nature of a mediastinal mass which takes up 67Ga after treatment is yet to be established. It is not clear that the statement “no mediastinal uptake of 201Tl following chemotherapy in a patient with Hodgkin’s disease is supportive evidence against the presence of viable tumor” (3) has a sound base. In fact, we believe that there is some uptake of 201Tl in the hyperplastic thymus of the patient described by Harris et al. (see Harris et al. Fig. 3), even if it is of definitely lower intensity than that of the 67Ga (3). A study which shows that 201Tl scintigraphy can be confidently used to determine if a mass represents thymic hyperplasia of the thymus after treatment or if a tumor will have to overcome a number of problems. The concentration of 201Tl in lymphoma after treatment may be lower than that of 67Ga (Fig. 1). Also, 201Tl is clearly taken up by the thymus after chemotherapy as shown in Figure 2, where there was no disease in the mediastinum in a patient with osteosarcoma after chemotherapy.

One has to remember that 201Tl is taken up by many normal tissues, such as striate muscle of the myocardium and hypermetabolic bone marrow, and by nonmalignant diseases, such as actinomycosis or candidiasis (13–19). It has to be shown in a sufficient number of patients with benign hyperplasia that there is indeed a marked difference in uptake between 67Ga and 201Tl. This difference has to be substantially more evident than that seen between 67Ga and 201Tl in cases where a lymphoma exists in order to differentiate benign and malignant masses after treatment. Determining when a difference in uptake indicates a benign or malignant lesion may be difficult. Moreover, the difference in uptake between 67Ga and 201Tl in hyperplasia in some patients may be less evident than in the case presented by Harris et al. (3).

A hyperplastic thymus is not the only problem. A relatively often observed but seldom discussed problem of 67Ga scintigraphy is bilateral hilar uptake in adults that may sometimes appear unrelated to treatment (20). If parahilar uptake appears before treatment and CT is normal, this symmetric uptake is probably of no clinical significance (20). However, parahilar 67Ga uptake in the chest is problematic after treatment, when the nature
FIGURE 1. An 8-yr-old boy with Hodgkin's disease of the nodular sclerosis type. After completion of chemotherapy, there was still disease in the mediastinum and left parahilar region. Gallium-67 scintigraphy (A) shows abnormal uptake in the upper mediastinum and left parahilar region. Thallium-201 scintigraphy (B) shows uptake in the same region but of definite lower intensity. The difference in the intensity of uptake is similar to the difference in intensity of 201Tl and 67Ga scintigraphy seen in Figure 3 (3).

FIGURE 2. A 15-yr-old girl with osteogenic sarcoma of the right leg after chemotherapy. Thallium-201 scintigraphy shows increased uptake in the thymus. There was no evidence of disease in the mediastinum.

of a residual mass seen on CT has to be determined. An escape of treatment or recurrence may be the reason for 67Ga uptake. If CT shows a marked improvement and 67Ga scintigraphy has the characteristic appearance of low intensity symmetrical hilar uptake, it is probably not indicative of active lymphoma and the patient can be assumed to have achieved a complete clinical response. Evaluation of response on CT, however, may be difficult and there are variations in 67Ga parahilar uptake intensity. A careful study to determine the value of 201Tl uptake in adults in cases of bilateral hilar uptake of 67Ga is still necessary.

Nuclear medicine techniques in oncology are useful only when they can add a dimension that imaging techniques such as CT or MRI cannot provide. This appears to be the case in monitoring the response to treatment of lymphoma or the recent attempt to determine the nature of a breast mass with 201Tl (21). On the other hand, CT and MRI provide suitable sensitivity and specificity for diagnosis and staging of most tumors.

Over the years, many radiopharmaceuticals have been suggested as “tumor-seeking” or “tumor-specific” agents. It is not yet clear, however, that a tumor-specific agent really exists, not even when theoretically it is a "magic bullet" (22,23). There are reports that 201Tl is taken up by a number of tumors, including lymphomas (13,24–31). If this uptake is indeed specific and 201Tl is not taken up by normal tissue or benign disease, it could provide a clinically valuable diagnostic tool. Specifically, 201Tl scintigraphy could be useful in determining the nature of a mass after treatment of lymphoma. There has been no evidence, however, for any specific mechanism which makes 201Tl a "tumor-specific" agent.

The expectation that MRI might be able to differentiate in vivo between neoplastic and normal tissue has not been realized, and it is not clear if it will be realized using nuclear medicine techniques. Heterogeneity is a hallmark of cancer (32) and overlap between normal tissue and cancer is large. For the highest prospective yield, only areas which do not overlap should be explored with radiopharmaceuticals. For evaluation of mediastinal and parahilar disease after treatment, a careful, objective evaluation in a large number of patients of the difference in uptake between 67Ga and 201Tl in lymphoma and in nontumor tissue will be necessary to establish the value of these radiopharmaceuticals.

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REFERENCES
3. Harris EW, Rakow JI, Weiner M, et al. Thall-


