Gallium-67 Uptake in a Mass of Benign Transformation Mimicking Recurrence of Nodular Lymphocytic Predominance Hodgkin's Disease

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Gallium-67 is now widely used in the management of lymphoma patients. It is not, however, tumor-specific and reasons for uptake in nonmalignant and premalignant lesions associated with lymphoma should be recognized. Gallium-67 uptake in a mass of progressively transformed germinal centers and sarcoid-like reaction, mimicking recurrence in a 31-yr-old man with nodular lymphocytic predominance Hodgkin's disease, is described. Gallium-67 was taken up on two occasions and a recurrence was suspected. On the first occasion, abnormal uptake was present in axillary lymph nodes and on the second in mediastinal and parahilar lymph nodes. Histology of the lesions on both occasions showed progressively transformed germinal centers and sarcoid-like reaction but no evidence of Hodgkin's disease (HD). Bilateral parahilar abnormal uptake of ^{67}Ga disappeared spontaneously without treatment after several months. The mass on CT regressed but did not disappear. This case demonstrates that the appearance of a new mass which takes up ^{67}Ga in lymphocytic-predominance HD during a continuous clinical remission does not necessarily indicate recurrence and the need for treatment. It suggests that a biopsy should be performed to determine the nature of the lesion.

Key Words: gallium-67 scintigraphy; lymphoma

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Tumor load is an important factor in the ability to successfully treat a recurrence of lymphoma (*1*). This makes the early diagnosis of recurrence an important aim of diagnostic imaging but such a diagnosis is difficult (*2*). Gallium scans, which are useful for monitoring responses to treatment (*3,4*) and predicting survival after treatment (*5,6*), were recently found to also be useful in diagnosing recurrence (*7*). In spite of the wide acceptance of gallium scintigraphy in the management of lymphoma patients, it is clearly not tumor-specific (*8*). False-positive gallium scans in lymphomas can be caused by uptake by normal structures such as bone, liver and spleen, or activity in the colon or by inflammatory and infectious processes. Sometimes the cause for nonmalignant uptake is not known. The parahilar region is a particularly problematic area in lymphoma patients with suspected recurrence (*9*). Gallium-67 may be taken up by a hyperplastic thymus (*10,11*) but in other cases the reason for uptake of ^{67}Ga in the parahilar regions is unknown (*12*).

We report another cause of nonmalignant uptake of ^{67}Ga. Since it was associated with the appearance of a new mass lesion, it could be differentiated from recurrence only by histology.

CASE REPORT

A 31-yr-old man with nodular, lymphocytic-predominance Hodgkin's disease (HD) in the right inguinal region achieved complete clinical remission after completing six courses of alternating MOPP/ABVD (mechlorethamine, Vincristine, Procarbazine, Prednisone, Doxorubycin, Bleomycin, Vinblastine, Dacarbazine) chemotherapy combined with radiotherapy. Gallium-67 scintigraphy showed the primary tumor in the inguinal region and became normal when a complete response was achieved. It was normal on four occasions during clinical remission. After 32 mo of continu-

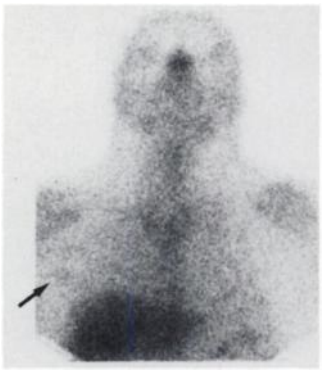

FIGURE 1. Routine follow-up ^{67}Ga scintigraph shows abnormal uptake in the right axillary region (arrow).

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FIGURE 2. Histology of the axillary lymph node (HE 50×). An area of typical PTGC seen in the center of the field shows two expanded follicles with no discrimination of the germinal center. On the left upper side, a normal follicle is seen.

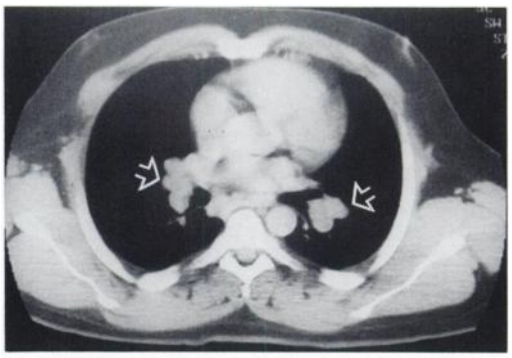

FIGURE 4. CT scan of the chest at the level of the hila shows bilateral lobular masses representing enlarged lymph nodes (arrows). After intravenous administration of contrast material, vascular enhancement is seen, whereas lymph nodes do not enhance.

ous clinical remission, a new area of ^{67}Ga uptake appeared in the right axillary region on a routine scan (Fig. 1).

An enlarged right axillary lymph node was then palpated on physical examination and was also demonstrated on CT. The mass was resected and histology showed progressively transformed germinal centers (PTGC) with reactive follicular hyperplasia (Fig. 2). There was no evidence of HD. The patient was not treated and remained well with no other evidence of disease. Six months later, prominent pathological bilateral parahilar uptake appeared on the gallium scan (Fig. 3). A CT scan showed a new bilateral hilar adenopathy (Fig. 4). The patient was still asymptomatic and other clinical restaging tests were negative for disease. Hilar lymph node biopsy by mediastinoscopy showed extensive infiltration by multiple sarcoid-like epitheloid cell granulomas with no evidence of HD (Fig. 5). The large mass on CT and intense uptake on ^{67}Ga scintigraphy were still worrisome. It was not clear that the benign findings on the histology obtained by biopsy were not due to sampling error. Right thoracotomy with multiple biopsies were therefore done to rule out recurrence of HD. Histology again showed massive granulomatous reaction obscuring the normal tissue intermingled with few foci of PTGC. Again, there was no evidence of malignancy.

The patient remained well during a further follow-up period of 7 mo. A gallium scan performed 4 mo after thoracotomy was normal (Fig. 6). A CT scan showed partial regression of the bilateral hilar lymphadenopathy (Fig. 7). The patient remained well and without treatment for 45 mo after achieving a complete response.

DISCUSSION

The nodular variant of lymphocytic-predominance HD is a distinct disease entity which is different from diffuse lymphocytic-predominance and other subtypes of HD (*13–18*). The histologic and immunophenotypic features distinguish nodular lymphocytic predominance HD from the other forms of HD. It has a B-phenotype originating from follicular center cells and its L and H variants of Reed Sternberg cells are distinctively different from the typical Reed Sternberg cells of other HD subtypes.

Controversy exists as to whether there is a unique clinical course for nodular lymphocytic predominance HD. Some investigators have described a different clinical course for nodular lymphocytic predominance HD. Others think that there is no correlation between this histological variant and the clinical behavior as compared to the other subtypes of lymphocytic predominance (*13–18*). The peak incidence of nodular lymphocytic predominance HD is in the fourth decade and it has a male preponderance. It is characterized clinically by indolent behavior with a high rate of relapse (*13,14,17*). Relapse can occur in sites other than those of initial disease. The relapse rate is evenly distributed during the first 10 yr after initial therapy. Despite this high recurrence rate, prognosis is favorable with

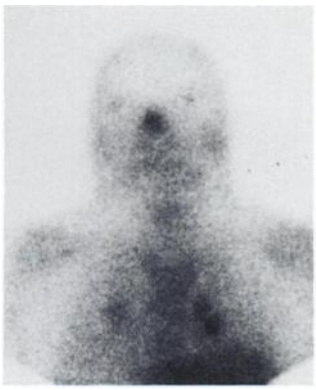

FIGURE 3. Gallium-67 scintigraphy 6 mo later shows bilateral prominent parahilar pathological uptake.

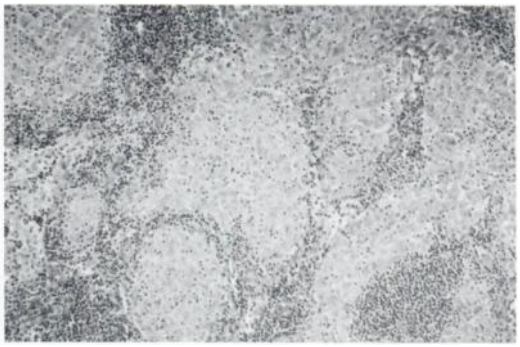

FIGURE 5. Histology of the hilar lymph node (HE 50×). Most of the lymphatic normal tissue is replaced by many epitheloid cell granulomas in a sarcoid-like reaction.

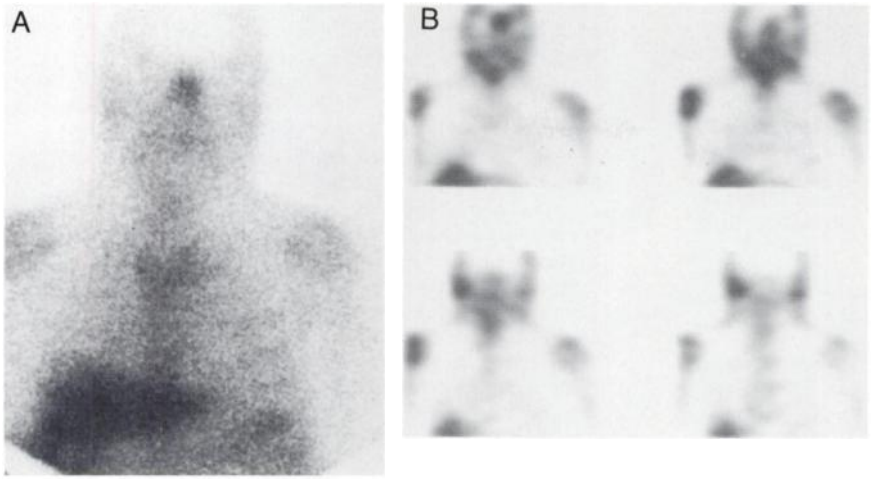

FIGURE 6. Normal ^{67}Ga scintigraph 4 mo after thoracotomy: (A) planar scintigraphy and (B) SPECT. The patient was asymptomatic and was not treated.

an overall survival rate of 99% during 5 yr and 77% during 15 yr (*14*).

The present case shows that in patients with nodular lymphocytic-predominance HD in continuous clinical remission, ^{67}Ga may be taken up by enlarged glands which are shown on CT but do not represent a true recurrence of disease. On histology of such glands, PTGC and sarcoid-like reaction are found. While the significance of this finding on the prognosis of the patient is not clear, the combination of ^{67}Ga uptake and a mass lesion indicates that a biopsy should be performed in order to clearly determine the histological nature of the lesion and differentiate it from true recurrence. There is no noninvasive way of differentiating a benign lesion from a recurrence. The histological changes in PTGC are mainly those of enlargement of the lymphatic follicles in the lymph node as a result of small lymphocytic infiltration into the germinal centers causing their expansion. These changes are usually focal and do not replace the whole of the lymph node.

The frequent association and the structural similarity between PTGC and nodular lymphocytic predominance HD (*13,14,17,19,20*) have been suggested to indicate that PTGC is a precursor of nodular lymphocytic predominance HD. This is especially so since there are cases when diagnosis of HD is avoided only because the L and H variants of Reed Sternberg cells are absent. Occasionally, subsequent biopsies will show a histology of nodular lymphocytic predominance HD (*13*).

There are, however, other studies which have shown that in many cases of PTGC, the patients did not develop HD after the diagnosis of PTGC (*21–24*). Currently it has been suggested that there are two separate variants of PTGC: one which is linked to HD recurrence and another which is probably unrelated to recurrence. It is not clear if ^{67}Ga is taken up in one variant or in both. Positive ^{67}Ga scans should therefore indicate that malignancy may follow. The uptake must also be separated from that in true sarcoid which may be associated with lymphoma.

In conclusion, this case indicates the need to recognize PTGC and sarcoid-like transformation as a cause for false-positive ^{67}Ga scintigraphy. When a new mass appears during continuous clinical remission, there is no noninvasive way to determine the nature of the lesion mass and histology should be performed to differentiate between benign and malignant lesions.

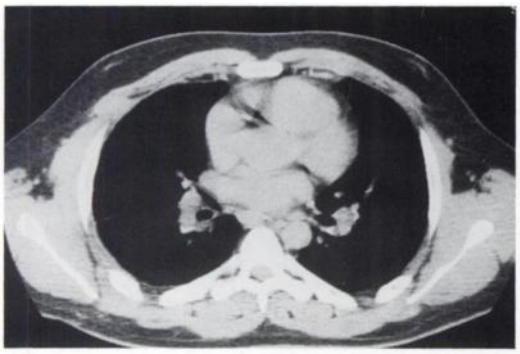

FIGURE 7. CT scan of the chest also obtained 4 mo after thoracotomy shows spontaneous regression in size of the hilar lymphadenopathy, although slight lymph node enlargement is still evident.

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