

# Incidental Uptake of In-111 Ibritumomab Tiuxetan in Surgically Treated Fracture

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## Abstract

In-111 ibritumomab tiuxetan pretherapy imaging is performed prior to radioimmunotherapy with Y-90 ibritumomab tiuxetan in patients with lymphoma in order to estimate the biodistribution of the radiolabeled antibodies. We report the case of a 61-year-old woman with relapsed follicular lymphoma. In-111 ibritumomab tiuxetan pretherapy imaging showed tracer accumulation in a surgically treated fracture of the left calcaneus as well as in the involved lesions. The patient had fractured her left calcaneus 6 months before the radioimmunotherapy, and fracture of the left calcaneus without lymphoma involvement had been revealed operatively at that time. Clinical features and magnetic resonance imaging (MRI) indicated an inflammatory response in the left heel. We concluded that this inflammation played an important role in the uptake on pretherapy imaging. It should be kept in mind that the inflammation is a differential diagnosis of lymphoma involvement in In-111 ibritumomab tiuxetan pretherapy imaging. To the best of our knowledge, this is the first case report of In-111 ibritumomab tiuxetan uptake in a surgically treated fracture.

**Keywords:** In-111, Ibritumomab, Fracture, Lymphoma

## 1. Introduction

In January 2008, radioimmunotherapy with Y-90 ibritumomab tiuxetan was approved in Japan. This is an effective treatment for refractory or relapsed non-Hodgkin's lymphoma [1]. It is composed of a radionuclide conjugated to the monoclonal antibody targeting CD20 on the surface of lymphocytes. The beta emission from Y-90 induces cellular damage in the target. In addition to that, radiation damage can be achieved in neighboring cells that not express the antigen or that compose poorly vascularized bulky tumors. The main toxicity is myelosuppression. In order to predict toxicities, estimating the biodistribution of the radiolabeled antibodies is important. The gamma emitter In-111-labeled ibritumomab tiuxetan is generally administered prior to the pure beta emitter Y-90-labeled ibritumomab tiuxetan because of the impossibility of obtaining a drug distribution image by the beta emitter. Patients with altered biodistribution (e.g. prominent bone marrow uptake) on In-111 ibritumomab tiuxetan pretherapy imaging cannot receive Y-90

ibritumomab tiuxetan.

Here we report a patient who underwent radioimmunotherapy with Y-90 ibritumomab tiuxetan for relapsed follicular lymphoma. In this patient, pretherapy imaging using In-111 ibritumomab tiuxetan demonstrated uptake not only in the involved lesions, but also in a surgically treated fracture. To the best of our knowledge, this is the first case report of In-111 ibritumomab tiuxetan uptake in a surgically treated fracture.

## 2. Case Report

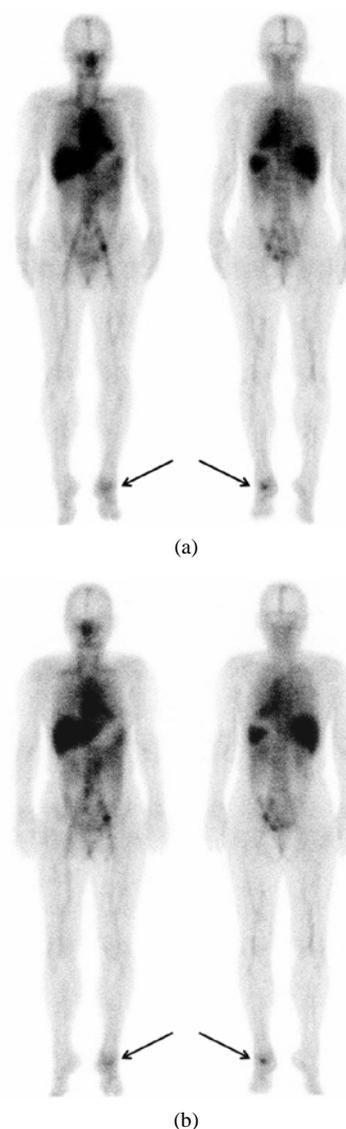
A 61-year-old woman was diagnosed with stage IVA follicular lymphoma, and complete remission was attained after eight cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy in another hospital. Four years after finishing R-CHOP chemotherapy, computed tomography (CT) demonstrated enlargement of her mesenteric and left internal iliac lymph nodes. During a 5-month "wait-and-see" period, CT showed an increase in the size of

these lymph nodes. Finally, she was admitted to our hospital to receive radioimmunotherapy with Y-90 ibritumomab tiuxetan. Laboratory data on admission (**Table 1**) including common blood count and blood chemistry were within normal limits except that the serum level of soluble interleukin-2 receptor (sIL2R) was 639 U/ml (the upper normal limit is 570 U/ml). F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT performed on the whole-body, except below the knees, showed abnormal uptake in the paraaortic, mesenteric, and left iliac lymph nodes. The maximal standardized uptake value (SUV max) among these lymph nodes was 10.4.

Initially, she received rituximab at a dose of 250 mg/m<sup>2</sup> to prevent In-111 labeled antibodies from binding to the CD20 antigens of normal B cells [2]. Subsequently, In-111 ibritumomab tiuxetan at a dose of 130MBq (the radiochemical purity was 98.8%) was administered in order to determine the indication of radioimmunotherapy with Y-90 ibritumomab tiuxetan. Whole-body anterior and posterior gamma camera scans were obtained at 48 hours after injection. These images demonstrated tracer accumulation in the paraaortic, mesenteric, and left iliac lesions compatible with the relapse of lymphoma demonstrated on the PET/CT. Furthermore, there was tracer accumulation in the left heel (**Figure 1(a)**). These findings on 48-hour images were same as those on 72-hour images obtained to assess tracer accumulation in the left heel (**Figure 1(b)**). She complained of chronic left heel pain on admission because she had missed a step and fractured her left calcaneus 6 months prior to admission. Radiograph on admission had demonstrated a faint sclerotic band in the fracture site. MRI was performed subsequently to confirm the cause of uptake in the left heel. Fat-suppressed T2-weighted MR images showed a hypointense line of the left calcaneus coincident with the fracture line, which was surrounded by an ill-defined high-signal-intensity area (**Figure 2**). These findings represent the fracture associated with bone marrow edema and suggested an inflammatory response at the bone fracture site [3]. Moreover, the surgical treatment performed following the fracture revealed that there was no lymphomatous tissue there. Thus, we concluded that uptake in the left heel on In-111 ibritumomab tiuxetan pretherapy imaging represented a surgically treated fracture with chronic inflammation. Radioimmunotherapy with Y-90 ibritumomab tiuxetan was performed 7 days following injection of In-111 ibritumomab tiuxetan, and the patient was discharged without any adverse reactions. PET/CT obtained 9 weeks after injection of Y-90 ibritumomab tiuxetan demonstrated that complete remission was achieved. Her left heel pain improved gradually. She had no pain as of 4 months after radioimmunotherapy.

**Table 1. Laboratory data on admission**

WBC	4430/ $\mu$ l	LDH	189 IU/l
neutro	73.0%	CRP	0.07 mg/dl
lymph	24.0%	sIL2R	639 U/ml
momo	2.0%		
RBC	$389 \times 10^4/\mu$ l		
Ht	35.9%		
Hb	12.1 g/dl		
Plt	$18.4 \times 10^4/\mu$ l		



**Figure 1. Whole-body anterior and posterior gamma camera scans at 48 h (a) and 72 h (b) after administration of In-111 ibritumomab tiuxetan show uptake in the left heel (arrows) in addition to that in the paraaortic, mesenteric, and left iliac lesions, and these findings are compatible with the relapse of lymphoma demonstrated on the PET/CT.**



**Figure 2.** A sagittal fat-suppressed T2-weighted MR image clearly depicts a hypointense line of the left calcaneus coincident with the fracture line (arrow), which was surrounded by an ill-defined high-signal-intensity area. These findings represent the surgically treated fracture associated with bone marrow edema and suggested an inflammatory response at the bone fracture site.

### 3. Discussion

We present here a case in which In-111 ibritumomab tiuxetan accumulated in a surgically treated fracture where inflammatory response was suspected to be persistent. To the best of our knowledge, there has been no report which showed In-111 ibritumomab tiuxetan uptake in inflammatory sites during radioimmunotherapy.

The mechanism of In-111 ibritumomab tiuxetan accumulation at the inflammatory site is still unknown. However, one possible explanation would be that this accumulation is due to the nonspecific accumulation of In-111 labeled antibody at the inflammatory site. Wegener *et al.* demonstrated that In-111 labeled nonspecific polyclonal immunoglobulin (IgG) scintigraphy is useful for detecting inflammatory and infectious foci [4]. However, the exact mechanism of the uptake of In-111 labeled human nonspecific IgG in inflammatory foci remains to be clarified.

Another possibility might be that the accumulation of In-111 ibritumomab tiuxetan is caused by accumulation of free In-111 in the inflammatory site. Indeed, there are a few descriptions of In-111 chloride uptake in both infected and noninfected ununited fracture sites [5,6], and in other inflammatory conditions such as abscess [7]. In the radiolabeling process of In-111 ibritumomab tiuxetan, small amounts of free In-111 chloride might dissociate

from anti-CD20 antibodies. Moreover, Claessens *et al.* reported that local retention of free In-111 in the inflammatory foci after dissociation from IgG was the most probable mechanism of In-111 labeled nonspecific polyclonal IgG uptake at the inflammatory site [8]. However, almost all free In-111 chloride should have bound to the diethylenetriaminepentaacetic acid (DTPA) included in the provided formulation buffer and then been excreted in the urine immediately after injection [9]. In addition, In-111 labeled antibodies are thought to be quite stable. Chinn PC *et al.* indicated that the average loss of Y-90 from the conjugate was 1% per day in the in vitro stability of Y-90 ibritumomab tiuxetan at 37°C [10], although the in vivo stability of In-111 ibritumomab tiuxetan has not been reported. Therefore, the amount of free In-111 chloride present would seem to be negligible.

We also suspected that the inflammatory response increased vascular permeability in the left heel and promoted the uptake there. To assess the increased blood flow in the left heel, whole-body anterior and posterior images were obtained at 72 hours after administration of In-111 ibritumomab tiuxetan. Although the radioactivity of mediastinal blood pool weakened on 72-hour images, tracer accumulation in the left heel on 72-hour images was the same as that on 48-hour images (**Figure 1(a)** and **(b)**). This indicated that uptake in the left heel was not merely a result of the increase of the blood pool.

The possibility of lymphoma involvement in the left calcaneus fracture site cannot be completely denied. However, the clinical course and MRI findings were compatible with inflammatory response. Moreover, the surgical approach had already revealed a fracture of the left calcaneus without involvement of lymphoma, although it was 6 months before the radioimmunotherapy. Biopsy of the left calcaneus would not be useful, since the presence or absence of lymphoma would not affect the decision to perform radioimmunotherapy. If whole-body PET/CT including the tips of the toes had been performed on admission, it might have demonstrated uptake in the left heel. However, it would be quite difficult to differentiate an inflammatory response from involvement of lymphoma on PET/CT.

In conclusion, we experienced a case in which In-111 ibritumomab tiuxetan was accumulated in the inflammatory site following the surgical treatment of fracture. When we encountered unusual or unexpected uptake in In-111 ibritumomab tiuxetan pretherapy imaging, it should be kept in mind that inflammation is a differential diagnosis of lymphoma involvement.

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