

Treatment of diffuse large B-cell lymphoma of the liver with yttrium-90 microsphere embolization

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SUMMARY

Background A 41-year-old male with a 4-year history of chronic hepatitis C presented with a 1-month history of abdominal pain, fatigue, weight loss, and night sweats.

Investigations Laboratory examinations, chest, abdomen, and pelvic CT scans, PET-CT scans, ultrasound-guided needle biopsies of liver lesions, bone-marrow biopsy, flow cytometry, and immunohistochemical staining for B-cell markers including CD20.

Diagnosis Chemoresistant diffuse large B-cell lymphoma, with gradual loss of CD20 antigen expression.

Management Embolization of hepatic tumors using yttrium-90 microspheres (Therasphere®, Theragenics Corporation, Buford, GA).

KEYWORDS CD20 antigenic loss, diffuse large B-cell lymphoma, primary hepatic lymphoma, radioembolization, yttrium-90 microspheres

CME

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the epidemiology and prognosis of non-Hodgkin's lymphoma.
- 2 Identify the differential diagnosis of non-Hodgkin's lymphoma of the liver.
- 3 Specify findings on liver imaging with different forms of liver cancer.
- 4 Identify possible effective treatments for chemotherapy-refractory diffuse large B-cell lymphoma.

Competing interests

The authors and the Journal Editor L Hutchinson declared no competing interests. The CME questions author CP Vega declared that he has served as an advisor or consultant to Novartis, Inc.

THE CASE

A 41-year-old male with a 4-year history of chronic hepatitis C presented to the emergency department with severe right upper quadrant pain, constipation, fatigue, decreased appetite, night sweats, and unintentional weight loss of 9 kg over 1 month. A liver biopsy sample taken 3 years earlier showed chronic hepatitis, portal inflammation (grade 1), and no fibrosis. Laboratory analysis revealed serum calcium levels of 3.37 mmol/l (normal range 2.1–2.62 mmol/l), normal albumin levels, and lactate dehydrogenase (LDH) levels of 85.02 mmol/l (normal range 11–21 mmol/l). The hypercalcemia was treated with intravenous fluids and pamidronate. Given the high likelihood of malignancy in this patient, CT scans of the chest, abdomen, and pelvis were ordered, which revealed

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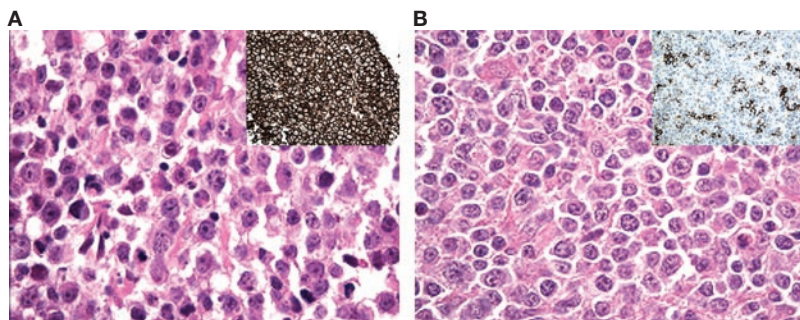


Figure 1 Images of liver biopsy samples in a patient with diffuse large B-cell lymphoma. **(A)** Biopsy sample from a porta hepatis lymph node showing diffuse large B-cell lymphoma, and immunohistochemical staining showing tumor cells strongly positive for CD20 (inset). **(B)** Liver biopsy sample showing diffuse large B-cell lymphoma, and immunohistochemical staining showing cells minimally positive for CD20 (inset). At each time point, there is a proliferation of large cells with regular to mildly irregular nuclei, vesicular chromatin, small but distinct single nucleoli, and moderate amounts of eosinophilic nucleoli.

a 13.4 × 10.0 cm mass involving the right hepatic lobe, along with lymphadenopathy of the porta hepatis, celiac, and retroperitoneal regions. A sample obtained by ultrasound-guided core biopsy of the porta hepatis lymph node showed diffuse large B-cell lymphoma (DLBCL; Figure 1A). Immunohistochemical staining demonstrated that the biopsy sample was strongly positive for CD20 (Figure 1A, inset), partially positive for bcl-2, and negative for CD10, CD3, and carcinoembryonic antigen. Bilateral bone-marrow biopsy samples were negative for signs of lymphoma. A PET-CT scan showed significant fluorine-18-labeled fluoro-deoxyglucose (¹⁸F-FDG) uptake in the right lobe of the liver and in the periaortic, porta hepatis, and cardiophrenic regions. The patient was diagnosed with stage IV-B DLBCL—which probably initially arose as a primary hepatic lymphoma—with a high–intermediate risk International Prognostic Index score.

The patient was treated with six cycles of rituximab, cyclophosphamide, vincristine, doxorubicin hydrochloride, and prednisone and showed a partial response. Contrast-enhanced PET-CT scan demonstrated decreased but persistent ¹⁸F-FDG uptake in the three liver lesions, and a new site of uptake in the portocaval region. Ultrasound-guided liver biopsy samples were nondiagnostic, revealing fibrosis. The patient refused open biopsy. It was concluded that the lesions were most likely to represent residual lymphoma, so the patient was treated with platinum-based second-line chemotherapy. After two cycles of rituximab, ifosfamide, carboplatin, and

etoposide (R-ICE), a restaging PET-CT scan revealed a very modest response, with decreased ¹⁸F-FDG uptake and overall size in one of the three right hepatic lobe liver lesions, and no change in the other two liver lesions. The patient was treated with a third cycle of R-ICE, after which autologous peripheral blood stem cells were collected. Unfortunately, a restaging PET-CT scan showed progressive disease, with a medial liver lesion that was increasing considerably in size.

On the basis of the patient's poor response to R-ICE and history of hepatitis C, there was concern that he might have concurrent hepatocellular carcinoma. The patient consented to an open liver biopsy and tumors in hepatic segments seven and eight were resected. Pathologic assessment of the biopsy samples revealed DLBCL and grade 1 chronic hepatitis C (Figure 1B). Interestingly, immunohistochemical staining showed that the neoplastic cells had only very minimal residual CD20 expression (Figure 1B, inset). Owing to the poor response to R-ICE, it was determined that the patient was not a candidate for high-dose chemotherapy with autologous stem-cell transplantation (SCT). As an alternative, he was started on third-line infusional chemotherapy that comprised a dose-adjusted regimen of etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin. After two cycles, a repeat PET-CT scan revealed stable disease within the liver and no evidence of malignancy outside the liver.

The patient was subsequently treated with palliative fourth-line chemotherapy consisting of gemcitabine, cisplatin, and dexamethasone. He showed disease progression after two cycles, with a new lesion measuring 4.7 cm in segment eight of the liver in addition to the two remaining lesions within segment seven (Figure 2A,B). The residual disease was confined to the liver, as assessed by PET-CT scan (Figure 2C,D). At this point, the patient developed severe right upper quadrant pain. Again, the patient was not considered a candidate for SCT because of insufficient chemosensitivity. Moreover, he was not a good candidate for radioimmunotherapy because of loss of CD20 expression on the neoplastic cells (Figure 1B, inset). As a result, localized therapies were considered; however, the patient was not a candidate for involved-field radiation therapy because of the risk of significant toxic effects in the adjacent liver tissue. He was, therefore, referred to an interventional radiology

department to be assessed for radioembolization with yttrium-90 microspheres (Therasphere®, Theragenics Corporation, Buford, GA).

Celiac, superior mesenteric, and hepatic angiograms revealed conventional hepatic arterial anatomy and two hypervascular tumors. The portal vein was patent. As required by protocol, a nuclear medicine shunt study was performed using a microcatheter in the right hepatic artery, and a lung shunt fraction of 14.6% was calculated. Given these findings, the patient was judged to be a suitable candidate for yttrium-90 microsphere embolization. Approval for compassionate-use treatment was granted by the FDA and the local institutional review board. The target liver volume was calculated using a triple-phase CT scan and a dedicated volumetric analysis. A dose of 10 GBq was calculated as the concentration necessary in order to deliver 100 Gy to the target tissue. After correction for decay and taking into account the lung shunt fraction, the injected activity was 2.28 GBq, which would correspond to a lung dose of 0.39 GBq. The patient was treated with individual 5 GBq doses in two separate arterial branches. Over the course of 2 weeks, the patient reported considerable improvement of his right-sided abdominal pain. Six weeks after yttrium-90 microsphere embolization, repeat CT scans demonstrated dramatic regression of the liver lesions (Figure 3A,B), with no evidence of abnormal ^{18}F -FDG uptake in the liver on PET scans (Figure 3C,D).

Unfortunately, the patient developed multiple new ^{18}F -FDG-avid right-sided pulmonary lesions. Samples obtained by subsequent CT-guided biopsy showed signs consistent with a diagnosis of DLBCL. The patient underwent 3 weeks of external-beam radiation therapy and demonstrated response within the radiation field; however, approximately 1 month later, he developed progressive disease in the thorax, including a large right pleural effusion and a pleural-based mass. Pleural fluid cytology results were consistent with large-cell lymphoma. Interestingly, the neoplastic cells had completely lost expression of CD20 and CD19 by this point, but were still clearly of B-cell lineage because CD79a, CD22, and kappa light chain continued to be expressed (details of these results can be found in Supplementary Figure 1 online). Palliative radiation therapy was administered and targeted to the pleural-based mass, an indwelling pleural catheter was placed, and other

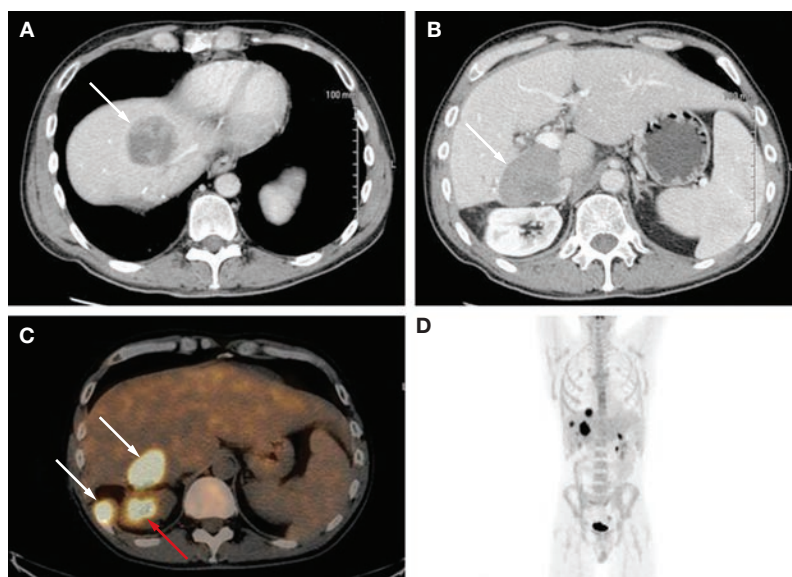


Figure 2 CT, PET-CT and whole-body PET images obtained prior to yttrium-90 microsphere embolization in a patient with diffuse large B-cell lymphoma. (A) CT image showing a prominent hypodense lesion in the dome of the liver (arrow). (B) CT image showing a hypodense lesion in the left lobe of the liver (arrow). (C) PET-CT fusion image showing liver tumors (white arrows) and normal ^{18}F -FDG uptake in the right kidney (red arrow). (D) Whole-body PET image of the patient, showing three FDG-avid liver lesions.

palliative measures instituted for approximately 3 weeks until the patient died.

DISCUSSION OF DIAGNOSIS

Approximately 58,000 cases of non-Hodgkin's lymphoma are diagnosed in the US annually, 34% of which are DLBCL.¹ Although outcomes for DLBCL have improved in recent years due to the advent of high-dose chemotherapy and autologous SCT,² and, more recently, due to the incorporation of the chimeric monoclonal antibody rituximab into treatment regimens,^{3–5} chemoresistance remains a considerable problem. Patients with chemo-refractory DLBCL have a very poor prognosis, the median survival being only 5–6 months even with the use of aggressive therapies, including SCT.^{6,7} As a result, such patients are not considered good candidates for SCT. Thus, novel therapies for chemo-refractory DLBCL are needed.

In patients with a history of hepatitis C, the development of hypercalcemia, elevated LDH levels, and hepatic lesions is highly suggestive of primary hepatic lymphoma (PHL), which is a rare subtype of B-cell lymphoma that is seen with increased frequency in patients with chronic hepatitis C infection. The predominant

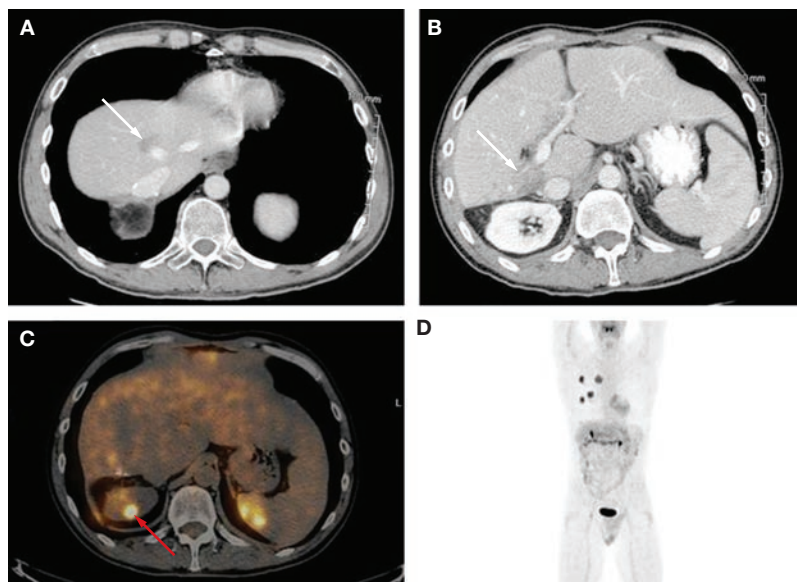


Figure 3 CT, PET-CT and whole-body PET images obtained 6 weeks after yttrium-90 microsphere embolization in a patient with diffuse large B-cell lymphoma. **(A)** CT image showing near complete resolution of the hypodense lesion in the dome of the liver (arrow). **(B)** CT image showing near complete resolution of the hypodense lesion in the left lobe of the liver (arrow). **(C)** PET-CT fusion image showing complete resolution of the liver tumors. The red arrow indicates normal ^{18}F -FDG uptake in the right kidney. **(D)** Whole-body PET image of the patient showing resolution of all sites of abnormal uptake within the liver, but four new ^{18}F -FDG-positive lesions in the right lung.

pathologic subtype of PHL is DLBCL. PHL is often associated with advanced age, elevated LDH levels, hepatitis C, and other co-morbidities that would have an adverse effect on prognosis.⁸ Aggressive treatment with combination chemotherapy, however, offers the potential for cure in a significant proportion of patients.⁹

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of patients with chronic hepatitis C presenting with constitutional symptoms, elevated LDH levels, hypercalcemia, and solid hepatic lesions on CT scan includes non-Hodgkin's lymphoma, hepatocellular carcinoma, metastatic carcinoma, and cholangiocarcinoma.^{8,10} On CT scans, lymphomatous liver lesions tend to be represented by hypodense regions, which over time can progress to become increasingly mass-like. Often there is coexistent lymphadenopathy and/or splenic involvement. Hepatocellular carcinoma is commonly found in patients with cirrhosis. Although the case patient did have chronic hepatitis C, he did not have a history of cirrhosis. Cholangiocarcinoma tends to be associated with

abnormalities of the biliary system, but no such abnormalities were demonstrated on CT scan in this case. For a definitive diagnosis, analysis of tissue biopsy samples is essential.

TREATMENT AND MANAGEMENT

Currently, patients with chemo-refractory DLBCL have relatively limited therapeutic options. Neither autologous nor allogeneic SCT offer notable benefit in this setting. For patients with relatively localized disease, involved-field radiation therapy can be considered; however, the use of external-beam radiation therapy to the liver is limited by the risk of radiation-induced liver disease. Although conformal-beam radiotherapy permits the administration of high levels of radiation to targeted lesions, exposure of the adjacent liver parenchyma might remain a limiting factor.

Novel systemic therapies such as radio-immunoconjugates have shown some promise in patients with chemo-refractory DLBCL.¹¹ The currently available agents, yttrium-90 ibritumomab tiuxetan (Zevalin®, Biogen Idec Inc., Cambridge, MA) and iodine-125 tositumomab (Bexxar®, Smithkline Beecham Corporation, Philadelphia, PA), target the B-cell antigen CD20. In the case presented, the neoplastic cells gradually lost CD20 expression, similar to previous reports in the literature,^{12–15} eliminating CD20-targeted radioimmunotherapy as an attractive treatment option.

This patient presented with normal liver function and hepatic reserve. Despite a lung shunt fraction of 14.6%, a total dose of 111 Gy was successfully delivered to the target liver volume. The tumors had been well visualized angiographically, so it was possible to deliver the yttrium-90 microspheres to segmental hepatic arterial branches instead of treating the entire right lobe. This segmental administration technique permitted the use of an increased amount of microspheres and thus the delivery of an effective radiation dose to the tumors. In addition, the hypervascularity of the tumors relative to normal tissue facilitated more selective deposition of the microspheres, increasing the effective delivery of the dose to the tumors. These factors permit the use of a higher and more selective tumor radiation dose with yttrium-90 microspheres than with external-beam radiation.

Although this patient ultimately died from progressive lymphoma, it is important to note that the liver was not a site of recurrence

following yttrium-90 microsphere embolization. This fact is of particular interest because before yttrium-90 microsphere treatment, there had been continuous liver lymphoma for a period of over 17 months, during which four different chemotherapy regimens were administered. Following these four chemotherapy regimens, the residual lymphoma was limited to the liver and the patient was experiencing severe right upper quadrant pain. This patient was not considered a candidate for additional chemotherapy, involved-field radiation therapy, radioimmunotherapy, or SCT; hence alternative therapies directed to the liver were considered. Not only did the patient derive considerable symptomatic benefit, but there was also no evidence of recurrence within the liver during the 5 months before his death.

CONCLUSIONS

To our knowledge, this Case Study is the first published paper describing the therapeutic use and outcome of yttrium-90 microsphere embolization for lymphoma. A recently published article details 138 patients with various hepatic tumors who were treated with yttrium-90 microsphere embolization.¹⁶ One of these patients had lymphoma; however, no information is presented regarding the response or outcome of that patient. Although our patient did eventually experience progression of lymphoma, yttrium-90 microsphere embolization provided both immediate and durable resolution of his liver lesions. Given the limited options for treating patients with chemotherapy-resistant lymphoma, yttrium-90 microsphere embolization could offer an additional treatment modality for patients with lymphomatous involvement of the liver. Whether this modality might provide greater long-term clinical benefit if administered earlier in the disease course should be evaluated in future studies.

Supplementary information in the form of a figure is available on the *Nature Clinical Practice Oncology* website.

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Competing interests

The authors declared no competing interests.

ERRATUM

The competing interest details for this Case Study, which appeared online on 16 September 2008, were incorrect. It was declared that the authors had no competing interests, however William S Rilling has declared competing interests with MDS Nordion, from whom he has received grant/research support. The other authors have declared no competing interests. [doi:10.1038/nponc1257]