CASE REPORT

Selective internal radiation therapy (SIRT) with yttrium-90 microspheres for unresectable intrahepatic cholangiocarcinoma

Vindya Abeysinghe,¹ Siva Sundararajan,² Luc Delriviere,² Jonathan Tibballs²

¹General Surgery, Royal Perth Hospital, Perth, Western Australia, Australia

²General Surgery, Sir Charles Gairdner Hospital, Nedlands, Australia

Correspondence to
Dr Vindya Abeysinghe,
vindya1143@gmail.com

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SUMMARY

Unresectable intrahepatic cholangiocarcinoma has a very poor prognosis despite various treatment options. The case presented describes the diagnostic challenges of a young pregnant woman with unresectable cholangiocarcinoma. The current treatment options for cholangiocarcinoma have limited evidence and high recurrence rate. Given the young age of this patient, selective internal radiotherapy was trialled with traditional chemotherapy with a clinically significant result. This case highlights the delays when diagnosing cholangiocarcinoma in younger patients and the possibility of selective internal radiation therapy in combination with chemotherapy as a potential first-line treatment for a complete response in unresectable disease.

BACKGROUND

Cholangiocarcinoma originate from the cholangiocytes that line the bile ducts. Although it only accounts for 3% of all gastrointestinal tumours, it is the second most common primary liver malignancy.¹ Apart from patients with primary sclerosing cholangitis, it is rare before the age of 40.² In 2012, the incidence in the USA was documented at 1.18 cases per 100 000.³ Surgery offers the best chance of curative treatment. However, less than 30% of patients have a resectable lesion at presentation. Patients with unresectable lesions have a poor prognosis with a median survival of 5–8 months.⁴ Their treatment options include systemic chemotherapy, external beam radiotherapy, transarterial chemoembolisation (TACE) and radiofrequency ablation (RFA). Selective internal radiation therapy (SIRT) with yttrium-90 microspheres in cholangiocarcinoma was first reported by Ibrahim *et al* in 2008.⁵ To our knowledge, this is the first report documenting complete metabolic response to yttrium-90 SIRT spheres treatment.

CASE PRESENTATION

A previously fit and healthy 33-year-old woman in her third trimester of pregnancy presented with pruritus of her hands and feet to her obstetrician. She was otherwise asymptomatic. Examination was unremarkable. Liver function tests (LFTs) showed normal bilirubin, mildly elevated transaminases and an alkaline phosphatase of 445 U/L (range 20–105 U/L). Abdominal ultrasound showed a

contracted gall bladder, no biliary dilatation and no focal hepatic lesions. A diagnosis of obstetric cholestasis was made and she was managed conservatively. She subsequently delivered a healthy baby.

At a follow-up consultation 3 months later, she was asymptomatic but had worsening LFTs with normal bilirubin but grossly deranged transaminases. Gamma glutamyl transferase was 1040 U/L (normal <40 U/L) and an alkaline phosphatase of 1424 U/L (normal 35–135 U/L). Alpha fetoprotein (AFP) was elevated at 534 U/L (normal <11 kU/L) and the cancer antigen 19–9 was 9 kU/L (normal <35 kU/L). She had an ultrasound that showed a 12×11 cm lesion in the right hepatic lobe. She then had a CT scan and core biopsy of the lesion.

INVESTIGATIONS

The biopsy comprises several irregular fragments of densely collagenous stroma containing small islands and trabecular malignant cells. The cells have large pleomorphic hyperchromatic nuclei and a mild to moderate amount of eosinophilic cytoplasm. Focal necrosis is noted. Immunostains show cytokeratin (AE1/3, Cam 5.2, CK7, CK19) positivity with negative staining for CK20, carcinoembryonic antigen, HSA (hepatocyte specific antigen), AFP, thyroid transcription factor 1 and breast markers (oestrogen receptor, progesterone receptor, human epidermal growth factor receptor 2). The biopsy findings would be in keeping with a primary cholangiocarcinoma (figure 1A, B).

The lesion was further characterised with MRI and positron emission tomography (PET) fluorodeoxyglucose (FDG), which showed intense avidity with central photopaenia suggestive of an aggressive lesion (figure 2A). She was discussed at the liver multidisciplinary meeting and the lesion was deemed unresectable. The options of chemotherapy and SIRT were explained to the patient.

TREATMENT

SIRT can cause radiation pneumonitis due to arterovenous shunting also known as liver–lung breakthrough. If the breakthrough is less than 10%, there is no reduction in yttrium-90 activity with an acceptable risk of radiation pneumonitis. The degree of breakthrough is determined by administering technetium-99m-macroaggregated albumin into the hepatic artery. The breakthrough in our patient

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Figure 1 (A) Core biopsy H&E stain, original ×200 magnification. Cholangiocarcinoma black arrow. (B) Core biopsy cytokeratin 7 stain, original ×400 magnification, consistent with cholangiocarcinoma.

was 2%. There were no aberrant vessels. She had four cycles of gemcitabine and cisplatin followed by SIRT. SIRT spheres of 1 GBq were instilled in the left hepatic artery followed by a further 1 GBq in the right hepatic artery. The patient did not have any treatment-related toxicity.

OUTCOME AND FOLLOW-UP

Follow-up MRI and PET FDG scan showed marked response (using Response Evaluation Criteria for Solid Tumors criteria) to SIRT, but there was still some residual activity in the periphery (figure 2B). She then had further six cycles of gemcitabine and paclitaxel and a second SIRT treatment with 1 GBq at 10 months postdiagnosis (figure 2C). Further PET FDG scans showed a complete metabolic response and reduction in size of the lesion on MRI and PET (figure 2D). The patient has remained well and is now 6 years postdiagnosis.

DISCUSSION

To date, there are only three reported cases of cholangiocarcinoma in pregnancy in the literature.^{6–8} Pruritus is a fairly common symptom in pregnancy that occurs in up to 20% of women.⁹ Intrahepatic cholestasis affects 1% of pregnant women in the USA but the incidence can be up to 28% in certain countries like Chile.¹⁰ These non-specific symptoms can easily be attributed to the pregnancy and disregarded. While cholangiocarcinoma is a rare entity in pregnant women, this report illustrates the importance of following up patients.

Cholangiocarcinoma has a poor prognosis due to its treatment refractory nature and often, delayed diagnosis. Overall, the 5-year survival is less than 5%.¹ After curative surgery, the 5-year survival is 14%–40%.⁴ Patients with unresectable disease have several options but almost all of them only offer limited improvement in survival compared with supportive care. There is no global consensus about the ideal treatment modality in cholangiocarcinoma.

For resectable disease, treatment involves either surgical resection or liver transplant. Liver transplant is usually not an option as most patients present with late-stage disease. The high recurrence rate of more than 70% within 5 years of transplantation and a median disease-free survival period of 8 months make this a controversial treatment option.¹¹ For unresectable disease, treatment can be either local or systemic treatment. Local treatment such as TACE is another modality that has been used with limited success. Park *et al* reported median survival of 12.2 months with TACE compared with 3.3 months in the supportive care group.¹² External beam radiotherapy is not tolerated well due to the relative radiosensitivity of normal liver parenchyma. Radiofrequency or microwave ablations are usually not feasible due to the large size of the lesion at presentation. Systemic treatment with chemotherapy is regarded as standard treatment in these patients. The Advanced Biliary Cancer (ABC-02) study using gemcitabine alone or in combination with cisplatin showed a higher median survival of 11.7 months with combination therapy compared with 8.1 months with monotherapy.¹³

SIRT using yttrium-90 microspheres involves injecting the β -emitting isotope into the hepatic artery supplying the tumour. The isotope becomes embedded in the tumour to emit local internal radiation.¹⁴ Although the use of yttrium-90 microspheres has been described since 1963, its use is still relatively new in cholangiocarcinoma.^{5 15–18} A recently published systematic review by Al-Adra *et al* identified 12 studies using yttrium-90 microspheres for unresectable intrahepatic cholangiocarcinoma. The median survival of the pooled results was 15.5 months.¹⁴ To our knowledge, there are no other case reports documenting the complete response of unresectable intrahepatic cholangiocarcinoma to yttrium microspheres 6 years postdiagnosis.

Several clinical trials are currently recruiting patients to determine the effectiveness of yttrium 90. A trial conducted by the Medical University of South Carolina (ClinicalTrials.gov NCT

Figure 2 (A) Pretreatment imaging. (B) Imaging post first SIRT. (C) Imaging post second SIRT. (D) Imaging 4 years postdiagnosis.

02512692) is aiming to determine the maximum tolerated dose of yttrium 90 when combined with gemcitabine and cisplatin in patients with unresectable intrahepatic cholangiocarcinoma. Sirtex Medical (ClinicalTrials.gov NCT 02807181) is conducting a multicentred prospective randomised controlled study to compare SIRT with yttrium-90 microspheres followed by cisplatin–gemcitabine versus cisplatin–gemcitabine alone for first-line treatment for unresectable intrahepatic cholangiocarcinoma. The results of these trials may eventually provide treatment guidelines for unresectable intrahepatic cholangiocarcinoma.

Learning points

- Cholangiocarcinoma in pregnancy is rare and can present a diagnostic dilemma due to the non-specific signs and symptoms.
- Selective internal radiation therapy in combination with chemotherapy has great potential as first-line treatment for unresectable intrahepatic cholangiocarcinoma.

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