Relapsed Hodgkin's lymphoma in pregnancy: A case review

Rhiannon George-Carey¹, Maryam Parisaei¹, Wiece Koniman¹, Micaela Pluckinski² and Jonathan Lambert²

Abstract

Hodgkin's lymphoma is rarely diagnosed in pregnancy, occurring in 1:6000 deliveries. However, improvements in survival and the use of less gonadotoxic treatments have increased the number of Hodgkin's lymphoma survivors becoming pregnant. Both de novo and relapsed Hodgkin's lymphoma in pregnancy pose difficult decisions for both clinicians and patients. This review discusses important diagnostic and treatment considerations of relapsed Hodgkin's lymphoma in pregnancy. We discuss a difficult case which illustrates these particular dilemmas and suggests the evidence behind different modalities of investigation and management.

Keywords

Cancer, high-risk pregnancy, oncology

Date received: 21 April 2017; accepted: 7 August 2017

Introduction

Overall, Hodgkin's lymphoma (HL) is rarely diagnosed in pregnancy, occurring in 1:6000 deliveries.¹ Improvements in survival and the use of less gonadotoxic treatments have increased the number of HL survivors becoming pregnant.² This is largely explained by its bimodal incidence, as the early peak coincides with women's childbearing years. Relapsed HL is defined as disease reappearance at prior sites and/or recurrence at any site following complete remission. It occurs in 10–15% with early stage disease and in 15–30% with advanced disease.³

The unique modulation of the immune system during pregnancy, which varies also with gestation and type of microorganism, results in different responses to disease.⁴ It used to be believed that women who were diagnosed with HL during pregnancy were at a higher risk of relapse and mortality; however, several studies have reported pregnancy to have no significant effect on the course of HL. A study by Lishner et al.⁵ found no evidence that pregnancy changes the biology of the tumour or that it postpones diagnosis. In addition, it did not report any metastases to placenta or fetus, and infants born to these women showed no difference in perinatal outcomes. In terms of future pregnancies, a study by Weibull et al.² found no evidence of pregnancy increasing the relapse rate of women in remission from HL.

This article will describe the presentation and clinical course of a patient previously treated for HL with a suspected relapse diagnosed during pregnancy. We will thereby illustrate some important considerations in its diagnosis and management.

Case presentation

In April 2016, a 22-year-old primigravida presented to the emergency department at 16 weeks' gestation complaining of genital pain and profuse, foul-smelling vaginal discharge. She had not been able to pass urine due to the pain. This was an unplanned pregnancy and she had no known history of sexually transmitted infections.

The patient's medical history included (i) type 1 diabetes with poor glycaemic control, (ii) recurrent abdominal wall abscesses, (iii) morbid obesity, (iv) tuberculosis with lymphadenopathy – diagnosed and treated with quadruple therapy in 2013 and (v) stage 3B nodular sclerosing HL diagnosed in December 2013, treated with ABVD therapy (doxorubicin, bleomycin, vinblastine and dacarbazine) before self-terminating after four out of six cycles. A positron emission

tomography (PET) scan following this showed a complete metabolic response. A multi-disciplinary team (MDT) discussion felt there was no benefit to giving further chemotherapy, or radiotherapy, at this stage.

Initial assessment revealed very tender and inflamed vulva and vagina with discharge and she was treated for severe vulval candidiasis. She required catheterisation under sedation in theatre because of the pain. Genital swabs later confirmed herpes simplex virus and chlamydia infections.

During her admission, she had an episode of desaturation. A computer tomography pulmonary angiogram (CTPA) excluded any pulmonary embolism (PE) but found evidence of anterior conglomerate mediastinal adenopathy. At this point her previous haematology-oncology team were therefore alerted.

The decision was made to investigate for possible relapsing lymphoma despite the pregnancy, and the patient was also commenced on prophylactic low-molecular weight heparin in light of her obesity, pregnancy and possible active cancer.

A whole-body magnetic resonance imaging (MRI) showed generalised small volume of her thoracic and supraclavicular lymphadenopathy, in keeping with relapse, but without any critical organ compression. MDT discussion agreed that, as the patient was stable, she could be carefully monitored for the remainder of the pregnancy with a view to starting second-line chemotherapy after delivery.

The patient delivered a baby girl by category 3 caesarean section at 32+1 weeks' gestation because of suspected intrauterine growth restriction. The birth weight, 1735 g, was in fact appropriate for the gestation. Her daughter was admitted to the Neonatal Intensive Care Unit for ventilation following signs of respiratory distress at birth. Other problems included neonatal hypoglycaemia and jaundice, and nasogastric tube insertion to establish feeds. On her 10th day, she had an episode of supraventricular tachycardia secondary to hypomagnesaemia which responded to ice therapy. An echo was arranged which

¹Department of Obstetrics and Gynaecology, Homerton University Hospital, London, UK

²Department of Haematology-Oncology, University College Hospital, London, UK

Corresponding author:

Rhiannon George-Carey, 17 Jameson Street, London W8 7SH, UK.

Email: r.george-carey@nhs.net

found a muscular ventricular septal defect for which no intervention was required.

Following delivery, a core biopsy of our patient's left supraclavicular lymph node confirmed the diagnosis of classical HL. She declined a PET but had a CT showing an anterior mediastinal mass caused by a confluence of lymph nodes measuring $7 \times 4.5 \times 2.5$ cm, and subcentimetre para-aortic lymphadenopathy. She commenced second-line chemotherapy with ifosamide, etoposide, epirubicin (IVE), prior to which she was educated on identifying early signs of infection. Two weeks later, she attended A&E with sepsis secondary to an axillary abscess. She did not return for her second chemotherapy cycle and has defaulted from follow-up.

Discussion

Many presenting symptoms of HL are similar to features of pregnancy, such as fatigue, anaemia and painless lymphadenopathy.^{6,7} Here, the patient was diagnosed following investigation for a suspected PE. Despite her medical history, relapsed HL was not considered prior to the CTPA result. There should be a high index of suspicion in such patients to limit any delay in diagnosis and to avoid exposing the fetus to radiation.

Diagnosis ideally consists of an excisional lymph node biopsy, and if relapsed HL is confirmed, restaging should be evaluated using the Ann Arbor system. This involves laboratory and imaging studies.⁶ In *de novo* HL, biopsy is used to determine histology and imaging to assess the extent of disease; in relapsed HL, biopsy can confirm that there is no change in histology and imaging can confirm that any abnormalities found represent active disease.⁸ In pregnancy, ultrasound or MRI should be used instead of the customary CT or PET scans. PET scanning is typically contraindicated in pregnancy. When it is indicated in pregnancy, it is advised to reduce the dose of radiation, to apply techniques such as 3D imaging to support the reduced dose, increased oral or intravenous hydration and increased voiding.⁹

Restaging is required to assess prognosis and guide treatment. Prognostic models are less well defined for relapsed HL compared to primary; relapse after complete remission has a better prognosis than refractory disease, as does remission duration of more than 12 months.¹⁰ Indicators for poor prognosis are remission duration of less than 12 months, late clinical stage and anaemia at time of relapse.¹¹ Management of HL in pregnancy must be individualised and decisions should be made jointly between obstetric, haematology-oncology and neonatology teams and the patient. The selection of treatment depends upon the trimester, the location and stage of disease, the duration of remission and the extent of prior therapy.^{3,12}

In *de novo* HL, beyond the first trimester, management options include observation, chemotherapy and radiotherapy. Radiotherapy can offer local disease control but is associated with teratogenesis and an increased risk of childhood malignancy.¹³ Chemotherapy during the first trimester can result in spontaneous abortion or major morphological abnormalities. In the latter trimesters, possible effects include intrauterine growth restriction, low birth weight, preterm birth and stillbirth.⁶ The most popular chemotherapy regimen used, in pregnant and non-pregnant groups, is ABVD – its administration is associated with minimal maternal complications or fetal detriment.¹⁴ Treatment can be deferred in patients with limited, stable and uncomplicated disease. This option allows for a complete work-up following delivery and accurate stage-appropriate management.

In certain cases, a delay in therapy may adversely affect maternal survival – for example, advanced disease in early gestation. In these cases, emergency termination of pregnancy (TOP) should be considered in view of the increased teratogenic effects of chemotherapy during early pregnancy.¹⁵ Another indication for emergency TOP is relapsed HL previously treated using combination chemotherapy,⁶ as described in this case. Relapsed HL is generally treated with salvage chemotherapy followed by a PET or CT scan to determine response.

Salvage therapy is high-dose chemotherapy associated with significant risks to the fetus, including spontaneous abortion as well as teratogenesis and an increased risk of childhood malignancy.⁶ In those who demonstrate a complete response, autologous haematopoietic cell transplantation (AHCT) is the preferred next step in treatment.³ Here, haematopoietic stem and progenitor cells are harvested and cryopreserved prior to chemoradiotherapy and later infused intravenously to provide marrow and immune function.¹⁶ Salvage therapy followed by AHCT cures approximately 50% of relapsed HL; in unsuccessful cases, immunotherapy is emerging as a promising treatment, including monoclonal antibodies and immune checkpoint inhibitors.¹⁷ Although our patient presented with relapsed disease, imaging investigation found no evidence of any critical organ compression. It was therefore decided that the pregnancy could continue with regular monitoring and to delay salvage chemotherapy until after delivery.

Weibull et al.² conducted a review of the Swedish Cancer Register in order to further explore the risk of pregnancy-associated relapse in HL survivors. They concluded that there was no increase in the relapse rate among women in remission. They did however note that there is a higher risk of relapse in the first two to three years following diagnosis and this should be taken into account when planning future pregnancies. Despite these findings, cancer survivors report fear of pregnancy-related tumour progression or recurrence.¹⁸ These fears must also be considered in the context of possible reduced fertility, particularly in older women, balancing declining fertility with a lower risk of relapse.

Studies show that women generally want the opportunity to have children after a cancer diagnosis and increasing numbers of HL survivors means discussions about cryopreservation and gonadotropin-releasing hormone (GnRH) agonist administration are of great importance.^{19,20} Studies have shown that GnRH agonists taken in parallel with chemotherapy improve ovarian function and future fertility potential.²¹ ABVD chemotherapy in *de novo* HL does not usually result in permanent infertility and these women may not require fertility preservation. In relapsed patients requiring salvage therapy, however, oocyte or embryo cryopreservation should be considered in all women prior to commencing treatment.²² The consideration should (i) establish if they are well enough to undergo ovarian stimulation and egg collection, (ii) ensure the procedure will not worsen their condition and (iii) assess that there is enough time available before starting cancer treatment.²³ The patient discussed here was offered, on both occasions, pre-chemotherapy consultation with the fertility team and the option to start on a GnRH agonist which she declined. She became pregnant two years after her HL diagnosis; she also had suboptimal treatment of her HL due to choosing not to complete treatment. Her risk of relapse was therefore higher and remains so because of her continued poor-engagement with treatment.

Conclusion

HL in pregnancy is rare and poses difficult decisions for both clinicians and patients. Relapsed HL, in particular, imposes important limitations on its management including imaging modalities and chemotherapy/immunotherapy regimens. A high index of clinical suspicion is required in pregnant patients with a history of HL presenting with the non-specific symptoms described here. Emergency TOP should be considered when a delay in therapy might adversely affect maternal survival. If treatment is delayed until after delivery, women should then be worked up with a repeat biopsy and restaging. Studies have been reassuring in showing that pregnancy has little or no effect on the course of HL and vice-versa. However, concerns remain for survivors regarding future fertility and family planning that need to be individually considered and addressed.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Guarantor

JL

Contributorship

The review was written by RGC with input from M Parisaei, WK and JL. The latter four authors were all heavily involved in the patient's care.

References

1. Stewart HL and Monto RW. Hodgkin's disease and pregnancy. *Am J Obstet Gynecol* 1952; 63: 570–578.
2. Weibull CE, Eloranta S, Smedby KE, et al. Pregnancy and the risk of relapse in patients diagnosed with Hodgkin lymphoma. *J Clin Oncol* 2016; 34: 337–344.
3. LaCasce AS. Treatment of relapsed or refractory classical Hodgkin lymphoma. *UpToDate*, www.uptodate.com/contents/treatment-of-relapsed-or-refractory-classical-hodgkin-lymphoma?source=related_link (2017, accessed 7 June 2017).
4. Mor G and Cardenas I. The immune system in pregnancy: a unique complexity. *Am J Reprod Immunol* 2010; 63: 425–433.
5. Lishner M, Zemlickis D, Degendorfer P, et al. Maternal and foetal outcome following Hodgkin's disease in pregnancy. *Br J Cancer* 1992; 65: 114–117.
6. Yahalom J and Horwitz S. Management of classical Hodgkin lymphoma during pregnancy. *UpToDate*, www.uptodate.com/contents/management-of-classical-hodgkin-lymphoma-during-pregnancy (2016, accessed 5 October 2016).
7. Mauch PM and LaCasce AS. Initial evaluation and diagnosis of classical Hodgkin lymphoma in adults. *UpToDate*, www.uptodate.com/contents/initial-evaluation-and-diagnosis-of-classical-hodgkin-lymphoma-in-adults?source=see_link§ionName=CLINICAL%20PRESENTATION&anchor=H78183236#H78183236 (2015, accessed 17 February 2017).
8. Collins GP, Parker AN, Pocock C, et al. Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma. *Br J Haematol* 2014; 164: 39–52.
9. Colletti PM. PET-CT in the pregnant patient. *Image Wisely*, www.imagewisely.org/~media/ImageWisely-Files/NucMed/PETCT-in-the-Pregnant-Patient.pdf (2012, accessed 10 February 2017).
10. Brice P. Managing relapsed and refractory Hodgkin lymphoma. *Br J Haematol* 2008; 141: 3–13.
11. Josting A, Franklin J, May M, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German's Hodgkin's lymphoma study group. *J Clin Oncol* 2002; 20: 221–230.
12. Mavroumatis CG, Daskalakis G, Papageorgiou I, et al. Non-Hodgkin's lymphoma during pregnancy – case report. *Eur J Obstet Gynecol Reprod Biol* 1998; 79: 95–97.
13. Donnelly EH, Smith JM, Farfan EB, et al. Prenatal radiation exposure: background material for counselling pregnant patients following exposure to radiation. *Disaster Med Public Health Prep* 2011; 5: 62–68.
14. Bachanova V and Connors JM. How is Hodgkin lymphoma in pregnancy best treated? *ASH Education Book* 2008; 1: 33–34.
15. Sanchez M, Pellicer B, del Puig Cozar M, et al. Hodgkin lymphoma in pregnancy: a case report. *Clin Adv Hematol Oncol* 2013; 11: 533–538.
16. Forman SJ and Nakamura R. Haematopoietic cell transplantation. *Cancer Network*, www.cancernetwork.com/cancer-management/hematopoietic-cell-transplantation (2015, accessed 5 July 2017).
17. Donato EM, Fernandez-Zarzoso M and De La Rubia J. Immunotherapy for the treatment of Hodgkin lymphoma. *Expert Rev Haematol* 2017; 10: 417–423.
18. Schmidt R, Richter D, Sender A, et al. Motivations for having children after cancer – a systematic review of the literature. *Eur J Cancer Care* 2014; 25: 6–17.
19. Letourneau JM, Ebbel EE, Katz PP, et al. Pretreatment fertility counselling and fertility preservation improve quality of life in reproductive age women with cancer. *Cancer* 2012; 118: 1710–1717.
20. Blumenfeld Z. How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist cotreatment in addition to cryopreservation of embryos, oocytes, or ovaries. *Oncologist* 2007; 12: 1044–1054.
21. Clowse MEB, Behera MA, Anders CK, et al. Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis. *J Womens Health* 2009; 18: 311–319.
22. RCP, RCR and RCOG. *The effects of cancer treatment on reproductive functions*. Report of a Working Party, UK, November 2007.
23. NICE. *Cryopreservation to preserve fertility in people diagnosed with cancer*. NICE Pathways, UK, 2016.