Rare disease

Plasma cell myeloma diagnosed in pregnancy

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Summary

Plasma cell myeloma (PCM) is an essentially incurable neoplastic disorder of terminally differentiated B cells. The neoplastic clone usually secretes a monoclonal protein in the serum or urine (the 'M band'). About 20% of PCM secrete light chains only, which are detectable in the urine as Bence Jones protein. The clinical picture is one of bone marrow failure, due to infiltration of the marrow by malignant plasma cells; renal failure due to damage to renal tubules by the excess light chains and pain due to lytic lesions of the bones. The outcome remains poor with median survival of 5 years.

BACKGROUND

Within the UK in 2006, 3987 people were diagnosed as having plasma cell myeloma (PCM), an incidence of 6.6/100 000; women are less likely to be affected.¹ The median age of diagnosis of PCM is 65 years, with 2% to 4% of cases under 40 years. Women presenting during the child-bearing years are extremely rare.²

This case is of a diagnosis of PCM made in pregnancy, only the 10th in the medical literature. We describe the antenatal, delivery and postnatal management of the pregnancy within a multidisciplinary team of obstetricians and haematologists.

CASE PRESENTATION

A 33-year-old Caucasian woman booked with her first pregnancy at 10 weeks' gestation. The patient had a medical history of polycystic ovaries, endometriosis and hypothyroidism. Previously, after 4 years of failing to conceive the patient had been given clomiphene; the pregnancy was conceived after the sixth cycle. There was no family history of note and the patient was an ex-smoker with a body mass index of 33.

Booking blood tests performed at 14 weeks' gestation revealed a platelet count of 79×10^9 cells/litre and haemoglobin of 9.3 g/dl with a normal white cell count. The differential diagnosis included idiopathic thrombocytopenic purpura, systemic lupus erythematosus and gestational thrombocytopenia (although the latter was thought very unlikely at 14 weeks). The plan was to repeat the blood tests including haematinics, an autoimmune screen and blood film in 1 week.

A week later the patient was reviewed and had evidence of morning sickness but was otherwise well. She stated she had pain in the right hip. Physical examination was unremarkable. Repeat blood tests showed persistent anaemia and thrombocytopenia, with normal haematinics. The blood film was reported as leucoerythroblastic; rouleaux, red cell poikilocytosis, circulating plasma cells and immature granulocytes were noted. A bone marrow biopsy was performed.

RESULTS

Urea, creatinine, electrolytes, liver function tests, were normal and virology tests were negative. Serum corrected calcium was raised at 3.0 mmol/litre (2.15–2.6 mmol/litre), lactate dehydrogenase 671 IU/litre and urate 408 μ mol/litre (150–350 μ mol/litre).

Bone marrow aspirate was technically difficult and the aspirate was haemodilute but immunophenotyping of cells demonstrated a clonal population (4%) of plasma cells (CD38, CD138 positive cells with λ light chain restriction). The trephine was reported as a diffuse infiltrate of abnormal cells, which on immunocytochemistry were proven to be plasma cells. Cytogenetic analysis did not reveal any karyotypic abnormalities associated with myeloma.

Serum immunofixation showed two large λ light chains measuring 7 and 4 g with immunoparesis. A 24-h urine collection detected 1.9 g protein (normal range 0–0.15 g/24 h), 95% of which was Bence Jones protein; β 2-microglobulin measured 2.5 mg/litre (1–2.2 mg/litre) and albumin was 40 g/litre (stage 1 disease by International Staging System).³

A limited skeletal survey was performed with did not show lytic lesions in the skull, humeri or femori. A diffusion MRI scan was of poor quality due to artefact but showed no other areas suspicious of lytic lesions in the pelvis, thorax or skull.

A diagnosis of light chain only PCM stage 1 (as per International Staging System (ISS)) was made.

OUTCOME AND FOLLOW-UP

Management and follow-up

The patient and partner were informed of the diagnosis and counselled regarding treatment options. Currently, the standard treatment in the UK for newly presenting PCM is induction with combination treatment with cyclophosphamide, thalidomide and dexamethasone (CTD), followed by peripheral blood stem cell collection and high dose melphalan with stem cell rescue. The patient was counselled as to limitations of treatment options and the poor maternal prognosis in pregnancy, but opted to continue the pregnancy. Therefore the CTD regimen could not be pursued.

due to the known teratogenicity of thalidomide and potential teratogenicity of cyclophosphamide (although cyclophosphamide would have been the second choice treatment had dexamethasone not succeeded). An alternative schedule was initiated, with fortnightly pulses of dexamethasone 20 mg on days 1–4. Enxoxaparin 40 mg daily, allopurinol and lansoprazole were given as supportive care with weekly review by the haematologists and obstetricians.

By 19 weeks' gestation the patient had received two cycles of steroids, and her platelet count had recovered to 106×10^9 cells/litre. The percentage of Bence Jones protein in the urine fell to 70% and was quantitated at 1.58 g/litre.

Regular review continued to show stable blood results up to 27 weeks. During this period an ultrasound scan of the fetus showed a head circumference on the 50th centile and normal umbilical artery Doppler scans. The multidisciplinary team planned for delivery at 34 weeks' gestation assuming the patient remained clinically stable.

At 27 weeks the platelet level fell to 88×10^9 cells/litre. An ultrasound scan of the fetus at 28 weeks showed an estimated fetal weight less than the third centile, but with normal Doppler scans and amniotic fluid index. Review at 29, 30 and 31 weeks was uneventful apart from the patient having occasional right hip pain that increased with movement. A hip radiograph taken at 29 weeks showed no abnormality.

At 32 weeks' gestation the patient presented with severe right hip pain and was admitted for symptom control. A 24-h urine sample was collected and Bence Jones protein quantified at 3.10 g/litre, consistent with disease progression. A fetal ultrasound scan performed during admission showed linear growth, and umbilical artery Doppler scans were within normal levels but showing increased resistance. Middle cerebral artery Doppler scans were normal.

Delivery was planned in 1 week due to the combination of persistently low platelet levels (which did not improve with steroid treatment), increasing bone pain indicating clinical progression of the disease, worsening fetal Doppler scans and increasing proteinuria. Until then the patient was requested to stay in hospital for blood pressure checks every 4 h, twice weekly fetal ultrasound scans, regular blood tests and analgesia.

At 33+4 weeks' gestation a planned lower segment caesarean section was performed under general anaesthetic, and a baby boy weighing 1.630 kg was delivered. Fetal cord blood gasses were normal and the estimated maternal blood loss was 440 ml.

Post delivery the patient was given conventional preferred treatment (CTD), namely thalidomide 50 mg once daily, cyclophosphamide 500 mg once a week and dexamethasone 20 mg for 4 days on days 1–4 and 12–15 of a 21-day cycle.

Despite delivery and regular analgesia the patient continued to experience pelvic and hip pain. A MRI scan showed widespread lytic lesions and a pathological fracture of the right pubic ramus was noted. A single fraction of palliative radiotherapy was administered to the affected area with good effect.

The patient received a total of four cycles of CTD chemotherapy and had a good partial response. She then went on to have successful peripheral blood stem cell collection and

received high-dose melphalan and stem cell rescue. She recovered well and is currently in complete remission from the myeloma. Consideration is being given to allogeneic stem cell transplant as the only potentially curative option for PCM.

DISCUSSION

The presentation of PCM in patients under the age of 40 years old is rare, and more so within pregnancy. There have been 16^{2–4–17} cases of myeloma in pregnancy, 9^{2–4–10} of which were diagnosed while the women were pregnant.

Using OVID (<http://www.ovid.com>), we conducted a Medline search restricted to the English language and with the key words 'Multiple Myeloma' and 'Pregnancy'. A total of 17 papers were retrieved.

Of the 16 pregnant women, 7 had been diagnosed and given treatment before becoming pregnant. Of the women diagnosed in pregnancy the presentation was either due to development of bony pain or made due to identification of a biochemical abnormality. Three of the nine patients diagnosed as having PCM in pregnancy had bone pain. Two described spinal cord compression^{2–4} and the other a pathological fracture of the neck of humerus.⁶

Of the other six patients, one was diagnosed at 15 weeks after being admitted for hyperemesis. On admission she was found to be anaemic, in renal failure and hypercalcaemic. This pregnancy was terminated at 19 weeks to enable treatment to begin.⁵ The other cases describe women that were anaemic but generally well and on further investigation were found to have PCM.

The literature search also revealed a paper that describes a woman, known to have PCM, having repeated positive pregnancy tests despite not being pregnant. The article described that through immunohistological stains it was revealed that the myeloma cells expressed immunoactive human chorionic gonadotrophin (hCG) and therefore PCM can cause positive pregnancy test results in a non-gravid woman.¹⁸

Throughout the pregnancy, fetal growth and development has been described as normal provided maternal health was maintained. Of the patients already diagnosed as having PCM and on treatment at time on conception, there were no fetal abnormalities described. The majority of cases were allowed to deliver at term by normal vaginal delivery. One case, as previously described, underwent a termination at 19 weeks, and one pregnancy was delivered at 34 weeks by caesarean section due to disease progression (multiple lytic lesions) and the need to start treatment urgently.

One of the cardinal signs of PCM is proteinuria. This, in regards to pregnancy, is a risk factor and sign of pre-eclampsia. There are no reports in the literature first of the risk to a patient with PCM developing pre-eclampsia or second, how it would be diagnosed and treated. Due to the known connection of pre-eclampsia with renal impairment, regular blood pressure readings were performed. In this case enoxaparin was given due to the risk of thromboembolism, due to the known prothrombotic nature of PCM.

Tavani *et al* performed a case-control study in 1997 assessing reproductive factors and the risks of developing lymphoma and myeloma. The study concluded that the immunological changes that occur in early pregnancy are

likely mechanisms for the protection of patients from the risk of developing Hodgkin's lymphoma but did not protect against PCM or non-Hodgkin's lymphoma.¹⁹

In the postpartum period complications of PCM appeared in the women, but all of the neonates appeared to do well. The papers describe that the monoclonal band produced by the mother with PCM freely crosses the placenta with one report noting concentrations of 2000 mg/litre in the cord blood of the fetus; however this does not appear to have an adverse effect on the fetus. Follow-up to 28 months of the baby revealed no problems and chromosomal studies of the cord blood revealed a normal karyotype of the baby.¹⁴ One case report observed that a neonate, delivered by uncomplicated, planned caesarean section at 34 weeks for maternal reasons, had seizures that were due to abnormal calcium regulation. The neonate's urine had no abnormal proteins, and serum protein electrophoresis revealed negative findings. After discharge on day 10 of life the baby had no further fits or complications.⁶

Although several pregnancies were conceived while being treated for PCM, including cyclophosphamide,¹⁴ urethane¹⁷ and α -interferon treatment,¹² no fetal abnormalities are reported. One case was delivered early, as was our case, due to disease progression and the urgent need to begin treatment. The postpartum complications of PCM described that lead to death are renal failure, haemorrhage and sepsis. One woman who was described as having monoclonal gammopathy of undetermined significance (MGUS). The pregnancy was uneventful, but trace amounts of Bence Jones protein were detected. This was put down to progression of MGUS rather than PCM. In the postnatal period the patient progressed to PCM with lethargy and bone pain. The woman was admitted once renal failure was detected and she became profoundly septic. A CT scan revealed extradural plasmacytoma, which eventually caused an intracranial haemorrhage.¹¹ Another case describes a woman being admitted post partum due to recurrent rib fractures and haemorrhage requiring blood transfusions. The patient died soon after.¹⁷

Learning points

- ▶ Plasma cell myeloma (PCM) is an incurable disease with an estimated median survival of 5 years for the mother.
- ▶ It is rare in patients under 40 years old, but with an increasing maternal age it is likely that the incidence of diagnosis within pregnancy will increase.
- ▶ PCM within pregnancy appears to have little effect on the fetus as long as maternal well-being is maintained.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Willmott F, Agarwal N, Heath M, Stevens J, Chakravarti S. Plasma cell myeloma diagnosed in pregnancy. *BMJ Case Reports* 2010;10.1136/bcr.04.2010.2901, date of publication

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