CASE REPORT

Fatigue and breathlessness in pregnancy: a rare and sinister cause

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SUMMARY

We describe a rare but sinister presentation of fatigue and dyspnoea in a 39-year-old woman at 16 weeks gestation. Blood tests and bone marrow aspirate confirmed the diagnosis of multiple myeloma. The patient was managed expectantly during pregnancy with plasma exchange and blood transfusion. The pregnancy continued without event; labour was induced at 35 weeks gestation and a healthy female infant weighing 3100 g was delivered vaginally following a 2 h, 5 min labour. The patient subsequently underwent six cycles of cyclophosphamide, thalidomide and dexamethasone (CTD) chemotherapy followed by an autologous stem cell transplant (SCT) and reduced intensity conditioning matched unrelated donor (RIC MUD) transplant.

BACKGROUND

Multiple myeloma is the second most common haematological malignancy in the UK (second only to non-Hodgkin's lymphoma). It is a neoplastic disorder of plasma cells that secrete a monoclonal immunoglobulin, known as a paraprotein, that is detectable on plasma immunoelectrophoresis and in the urine as Bence-Jones protein.^{1 2} It is a disease that is predominant later in life, with the median age at diagnosis being 65 years.¹⁻³ Development of the disease before the age of 40 years is extremely unusual, accounting for only 2-4 cases per 100.^{1 3} Furthermore females are less likely to develop the condition⁴ making presentation during pregnancy vanishingly rare, though an increasing number of cases have been reported in the literature over recent years.⁵

CASE PRESENTATION

A 39-year-old woman presented at 16 weeks gestation of her second pregnancy with shortness of breath and fatigue. The dyspnoea was progressive in nature and was exacerbated by exertion. The patient's general physician (GP) felt that her dyspnoea was unusually severe for a patient of 16 weeks gestation.

The medical history included polycystic ovarian syndrome, for which she had been taking co-cyprindiol (Dianette). She had been prescribed oral folate and ferrous sulfate from the beginning of the pregnancy. There was no history of pre-existing cardiorespiratory disease and she denied any recent infections, haemoptysis or bone pains.

Family history was unremarkable with two healthy middle-aged siblings. She had never smoked and rarely consumed alcohol. She has one

previous child; a girl aged 4 at the time of presentation.

Examination at presentation was unremarkable with normal heart sounds and chest auscultation.

INVESTIGATIONS

Routine blood tests indicated a microcytic anaemia with a haemoglobin of 103 g/L. White cell count and platelets were normal. Urea, creatinine and electrolytes were within normal limits. Liver function tests (LFTs) were normal except for a markedly raised total protein.

The elevated total protein prompted the patient's GP to request serum electrophoresis which demonstrated an IgG paraprotein of 44 g/L with low IgA and low IgM levels. Bence Jones protein was detected in the urine. Following this result, an urgent referral to haematology was made.

A bone marrow aspirate confirmed the diagnosis of multiple myeloma, showing pathognomically elevated plasma cells (45%).

DIFFERENTIAL DIAGNOSIS

The key to making a diagnosis is to determine whether the shortness of breath is a symptom of pregnancy, caused by progressive diaphragmatic splinting from a gravid uterus and progesterone-induced hyperventilation. This should be a diagnosis of exclusion where there is no underlying cardiorespiratory disease.

A thorough history, systems inquiry, examination and chest X-ray may help exclude more common causes such as underlying asthma and lower respiratory tract infection. Anaemia in pregnancy is another common cause of dyspnoea and fatigue. Routine blood tests including urea and electrolytes (U&E), full blood count (FBC) and LFT should be ordered to exclude the latter and to investigate for rarer pathology.

TREATMENT

The patient was urgently referred to the Joint Obstetric and Haematology Clinic. Following discussion it was agreed that termination of pregnancy was not indicated and that definitive treatment could safely be deferred at this time. Management was therefore expectant while observing for end organ damage in the form of progressive anaemia (her haemoglobin was 103 g/L at presentation), hypercalcaemia and renal failure.

The patient was reviewed regularly by haematology and obstetrics. Two weeks later her haemoglobin had dropped to 93 g/L and it was felt that plasma exchange should be started and repeated

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every 2–3 weeks while monitoring paraprotein levels. This was essential to prevent plasma viscosity rising dangerously high and compromising placental blood supply to the fetus. Following plasma exchange the patient responded well and her paraprotein level fell from 46 to 13 g/L. Nevertheless her anaemia worsened (haemoglobin 80 g/L) necessitating a 2 unit blood transfusion.

Obstetrically the pregnancy proceeded well. Her symptoms were greatly improved post-transfusion. Ultrasound scan at 28 weeks confirmed good fetal growth. Ongoing discussions across the multidisciplinary team agreed that the pregnancy should continue. Delay beyond 32 weeks was felt to be beneficial, both in terms of facilitating induction/vaginal delivery and reducing the risks of prematurity.

Ideally, it was hoped that delivery could be delayed past 35 weeks, but this needed to be balanced against the risks of continuing to not actively treat the underlying disease. Decisions were further complicated by the diagnosis of gestational diabetes.

At 31 weeks of pregnancy rising levels of serum paraproteins (despite the use of regular plasma exchange) necessitated a single treatment with high-dose fluorinated corticosteroids, dexamethasone 10 mg, at 31 weeks gestation, given as inpatient with blood sugar monitoring. Concerns were expressed regarding the effects of repeated steroids on the unborn child (reduced birth weight and/or abnormal neuronal development).^{6,7} In addition there were ongoing concerns regarding venous thromboembolism (already a significant risk by virtue of the procoagulant state of pregnancy itself). She was therefore started on thromboprophylaxis—low molecular weight heparin; Tinzaparin 4500 units, subcutaneously, once daily. Chemotherapy was also considered at this stage but declined by the patient because of concerns about her unborn child.

OUTCOME AND FOLLOW-UP

Despite the problems the pregnancy was permitted to continue to 35 weeks gestation when labour was successfully induced. A healthy female infant weighing 3100 g was delivered vaginally following a 2 h, 5 min labour, complicated by a post-partum haemorrhage of 800 mL.

Worsening back pain (initially noted at 32–34 weeks gestation and partly relieved by delivery) was formally assessed within the puerperium. Lumbar X-ray confirmed several vertebral crush fractures but no typical lytic lesions and the patient was started on intravenous zoledronic acid.

Following delivery the patient underwent six cycles of CTD (cyclophosphamide, thalidomide and dexamethasone) chemotherapy and an autologous stem cell transplant (SCT) the following year. Approximately 6 months later she underwent a reduced intensity conditioning matched unrelated donor (RIC MUD) transplant and was started on immunosuppression.

Eleven months post-SCT she remains in remission though has developed both oral and vaginal graft versus host disease and endogenous depression.

DISCUSSION

The evaluation of shortness of breath in adult patients can be difficult, given the many possible causes. It is especially challenging in pregnant patients, when dyspnoea is a common complaint affecting 60–70% of women. It usually begins in the first or second trimester and is exacerbated by rest rather than exercise.⁸ It is usually mild and rarely incapacitates the woman. The causes are varied and can be solely due to pregnancy itself, in the form of 'dyspnoea of pregnancy', or may be the result of underlying disease. 'Dyspnoea of pregnancy' should be a

diagnosis of exclusion, particularly when severe or of sudden onset. A thorough history, systems enquiry, examination and appropriate investigations are crucial in establishing a diagnosis and for excluding significant pathology, particularly pulmonary embolism. Anaemia of pregnancy is a common cause of more gradual onset of breathless and fatigue.

In this case the GP who initially saw our patient felt that the dyspnoea was 'more severe than usual' and quite rightly felt that underlying pathology needed to be excluded before this was labelled as 'dyspnoea of pregnancy'. The National Institute for Health and Care Excellence (NICE) guidelines state that FBC should be taken at booking appointment and at 28 weeks⁹ and the British Committee for Standards in Haematology recommend a further FBC being taken if the patient presents with symptoms of anaemia; the commonest symptoms being dyspnoea and fatigue.¹⁰

As a screening assessment for additional yet rarer causes of dyspnoea it is generally recommended that U&E (to exclude metabolic causes) and thyroid function tests (TFTs) (if hyperthyroid or hypothyroid is suspected) should be performed. Erythrocyte sedimentation rate is a non-specific marker of disease and is also routinely raised in pregnancy so it is of little practical use in this instance.

Furthermore, though not usually included as a screening test, it was the LFTs that proved invaluable in the index case and would perhaps serve as a useful addition to the already accepted screen. It was the abnormally raised total protein result that prompted further investigation which in turn led to an urgent referral and prompt diagnosis.

Other simple investigations that may be performed in primary care include ECG to exclude a cardiac cause of breathlessness. Consideration could also be given to requesting secondary care investigation such as chest X-ray or echocardiogram but an initial work-up of simple investigations should be performed first and foremost. In this case, further investigation by primary care was unnecessary and waiting for further tests to be performed may have delayed the referral.

It is important that all healthcare professionals caring for pregnant women are vigilant for the rare but potentially life-threatening causes of the common symptoms of pregnancy. It is only by having a high index of suspicion that more significant pathology will be detected. Morbidity is the 'morbidity of delay' both for the mother and the baby.

The use of chemotherapy to treat maternal malignancy during the antepartum period has become increasingly common practice. There have understandably been concerns about the effects of chemotherapy on the developing fetus. Clearly the greatest risks are during the essential stages of organogenesis of the first trimester and chemotherapy use during this period has been reported to have a 10–20% risk of major congenital abnormalities and a 33% risk of adverse pregnancy outcome. The risks, however, appear to diminish as pregnancy advances. The major risks of chemotherapy administered in the second and third trimesters are low birth weight, intrauterine growth restriction, premature birth and still birth.¹¹

A 2012 study published in the *Lancet* found there was no increase in central nervous system or cardiac abnormalities and no evidence of detrimental effect on growth or general health. Indeed, it was found that prematurity has the biggest impact on the fetus, causing impaired cognitive development. This obviously has implications for management as the evidence points against inducing women prematurely to have chemotherapy. The conclusions of this study were corroborated by another trial that looked in to the long-term effects of chemotherapy on

fetuses whose mothers were treated with chemotherapy for haematological malignancy.¹²

Clinicians must, however, remain extremely cautious in the consideration and use of chemotherapy in the second and third trimesters and a full and frank discussion must be had with the patient with full consideration of the risks and benefits with clear documentation of this in the medical notes.

To date there have been 26 reported cases of myeloma associated with pregnancy. Most presented with bone pain and/or anaemia. While the mother's outcomes varied widely, all the delivered newborns were healthy. In the first reported case in 1965 the disease was advanced at diagnosis and the woman died within 9 months of delivery. In this most recent case from 2011, diagnosis was prompt and the patient remains in remission at approximately 3 years since presentation.

The increasing number of reported cases of myeloma in pregnancy suggests either an increasing incidence or increased skill in identifying and treating myeloma in pregnant patients. Despite increased reporting there remains a lack of consensus

regarding treatment strategies. Myeloma in pregnancy therefore remains a diagnostic and therapeutic challenge for general practitioner, obstetrician and haematologist. It is likely that prompt diagnosis and an individualised multidisciplinary approach to therapy and management will produce the best outcomes for mother and baby.

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Contributors LB is a consultant obstetrician at St Mary's Hospital in Manchester. She was one of the key consultants involved in the MDT and decision-making of the published case. JQ and AK are both foundation year 2 doctors who have an interest in maternal medicine. They liaised with LB in researching and writing up the case.

Competing interests None.

Patient consent Obtained.

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Learning points

- Dyspnoea and fatigue are common presentations during pregnancy and it is vital routine blood tests (ie, urea and electrolytes, full blood count, thyroid function tests and perhaps liver function test) are taken to aid in excluding sinister causes.
- *Dyspnoea of pregnancy* is more likely to produce symptoms 'at rest rather than on exertion'.
- A high index of suspicion for rare causes can avoid inappropriate dismissal of symptoms as physiological—particularly when unusual and/or severe. The latter should be a diagnosis of exclusion.
- Diagnosis of multiple myeloma in pregnancy does not necessitate termination of the pregnancy.
- A multidisciplinary, yet individualised approach to management of complex haematological–obstetric problems is essential for a good outcome for mother and baby.

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