Case Report

See http://www.oxfordjournals.org/our_journals/ndtplus/

Renal failure complicating myeloma in pregnancy

James C. Lee¹, Ross S. Francis², Steve Smith³, Richard Lee¹ and Coralie Bingham¹

¹Royal Devon and Exeter Hospital, Exeter, UK, ²Nuffield Department of Surgery, John Radcliffe Hospital, Oxford, UK and ³Torbay Hospital, Torquay, UK

Keywords: immune surveillance; MGUS; myeloma; myeloma kidney; pregnancy; renal failure

Introduction

Multiple myeloma (MM) is a malignancy of plasma cells characterized by the production of a monoclonal immunoglobulin, or paraprotein, which can be detected in the serum and/or urine. The clinical features include bone pain, anaemia, hypercalcaemia, renal impairment, recurrent infections associated with immunoparesis, abnormal bleeding tendency, amyloid and hyperviscosity syndrome. In most cases the cause is unknown, although there is evidence for certain aetiological factors including monoclonal gammopathy of undetermined significance (MGUS) [1]. MGUS is characterized by the presence of a paraprotein in the serum but <10% plasma cells in the bone marrow. There are no bone lesions or immunoparesis. The paraprotein concentration is usually <20 g/l and stationary, whereas in myeloma it is >20 g/l and rising. Despite its association with myeloma, the factors involved in the progression of MGUS to myeloma are not well understood [1].

Myeloma developing under the age of 40 years is very rare and there have been only nine cases reported of myeloma complicating the pregnancy or the post-partum period [2–10]. We report the first case of renal failure in a patient in whom pregnancy was associated with the progression of MGUS to myeloma.

Case

The patient, a 32-year-old Caucasian female, initially presented with a low titre IgG lambda paraprotein (3.2 g/l) when she was 25 years old. At this time a bone marrow examination demonstrated normal marrow with <2% plasma cells, and a skeletal survey was unremarkable. Her renal function, C-reactive protein and β-2-microglobulin were normal. She was diagnosed as having MGUS. For the next 6 years her paraprotein remained stable (range 2.7–4.4 g/l). When she was 31 years of age her paraprotein rose to 20.8 g/l and she developed a small urinary Bence Jones protein leak. At this time a skeletal survey remained unremarkable and her bone marrow showed that 9% of all nucleated cells were plasma cells. Cytogenetics showed a normal female karyotype and no common myeloma-associated abnormalities. Her renal function, C-reactive protein and β-2-microglobulin remained normal. An MR scan of her spine was unremarkable. She, therefore, did not fulfil the criteria for diagnosis of myeloma but rather a progressive MGUS. She conceived later that year, after a number of years of infertility, including a failed course of IVF. When she was 3 months pregnant her paraprotein was 28.7 g/l. She was commenced on low dose aspirin due to her raised plasma viscosity of 3.17 (normal range 1.50–1.72). Her paraprotein levels were closely monitored throughout the remainder of the pregnancy. Her paraprotein stabilized at around 30 g/l (range 28.7–34.1 g/l) with a Bence Jones protein of 1.2 g/24 h. Throughout her pregnancy her renal function also remained stable (Creatinine 65–75 µmol/l) and hence no attempts were made to examine renal histology. She subsequently gave birth to a healthy female infant.

In the post-partum period she reported increased lethargy, reduced appetite, nausea and vomiting, weight loss and back pain. She attributed these symptoms to the problems associated with her pregnancy and further specialist review was not initially requested. She also noted two ‘lumps’ on the right side of her forehead. Three months after delivery her symptoms worsened, she became oliguric and blood tests revealed that she was having renal failure with a creatinine of 3190 µmol/l (normal range 40–97 µmol/l), urea 49.0 mmol/l (2.5–6.6 mmol/l), calcium 2.88 mmol/l (2.05–2.60 mmol/l), urate 365 mmol/l (0.1–0.4 mmol/l), haemoglobin 6.2 g/dl (11.0–15.0 g/dl) and platelets 95 x 10^9/l (150–400 x 10^9/l). Urinalysis showed a proteinuria of 3.4 g/l, haematuria of 9 g/l and no casts. Her renal biopsy showed features of acute tubular necrosis with focal interstitial fibrosis. She was treated with continuous renal replacement therapy and her paraprotein levels remained stable at around 30 g/l. She subsequently had a further renal biopsy which showed features of chronic renal failure consistent with the myeloma kidney. She was started on bortezomib and showed a partial response with a reduction in her paraprotein to 10.2 g/l. She eventually had a complete remission of her myeloma with a paraprotein level of 1.2 g/l and her renal function returned to normal range (Creatinine 65–75 µmol/l) and she was ultimately discharged home.
1035 (135–360 μmol/l), haemoglobin 5.9 g/dl (12.0–15.0 g/dl), white cell count 10.0 (4.0–10.0 × 10⁹/l), platelets 347 (150–400 × 10⁹/l), CRP 100 mg/l (<3 mg/l), ESR 73 mm/h (<20 mm/h), INR 1.4 and APTR 1.1.

On admission to hospital she was apyrexial and dehydrated with a bounding pulse, rate 90 beats/min, and a blood pressure of 140/70. She was noted to have an early systolic murmur. She had tenderness over her lower ribs on the right side and she also had two palpable lumps on the right side of her forehead. She underwent urgent haemodialysis and a blood transfusion via a femoral dialysis catheter. At this stage her paraprotein was 41.1 g/l and her Bence Jones protein was unmeasurable due to interference from the IgG detected in her urine. A repeat bone marrow examination revealed a marrow consisting entirely of plasma cells. A skeletal survey showed multiple lytic lesions within the skull, both humeri, right clavicle, both femurs, several ribs and T9, T11 and T12 vertebrae. A CT scan of the head confirmed multiple lytic lesions involving the vault and also demonstrated an extradural mass associated with a lytic lesion breaching the inner and outer table of the skull vault felt to represent a plasmacytoma (Figure 1). A renal ultrasound demonstrated kidneys of normal size. It was therefore felt most likely that myeloma kidney was the cause of her renal failure, she was too unwell to undergo a renal biopsy. A renal screen was performed to attempt to identify another cause for her renal failure. This incorporated antinuclear antibodies (ANA), extractable nuclear antibodies (ENA), antineutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane antibody and hepatitis B and C serology. All of the above were negative except for the c-ANCA which was positive. However, ELISA tests for ANCA antigens, myeloperoxidase and proteinase-3, were negative. She was treated with high-dose oral dexamethasone for 4 days and commenced on plasma exchange. She received a total of four, 4 l plasma exchanges over 5 days in addition to the regular haemodialysis. She was also treated with allopurinol in view of her hyperuricaemia and with pamidronate for hypercalcaemia. Four days after admission, her femoral dialysis catheter was changed for an internal jugular dialysis catheter. On the same day she had an episode of pyrexia to 38.8°C and her CRP was noted to have risen to 431 mg/l. She complained of pleuritic chest pain and a chest X-ray revealed the presence of bilateral pleural effusions. She was commenced on a combination of oral fucidin, and intravenous clindamycin and imipenem. Over the next 48 h she became confused and following a further episode of pyrexia and CRP rise to 431 mg/l, the internal jugular dialysis catheter was removed and she received a dose of intravenous vancomycin. She also received intravenous vitamin K as her INR had risen to 1.6 with an APTR of 1.39. Her CRP fell to 279 mg/l after treatment with vancomycin. It was planned to start her on chemotherapy with Vincristine, Adriamycin and Dexamethasone for her myeloma once she had recovered from the sepsis. Plasma exchange was stopped because she was septic. Blood cultures grew *Staphylococcus aureus* as did the tip of her femoral line which had been removed. In view of the positive blood cultures her clarithromycin was stopped, and she was changed to a combination of oral fucidin, and intravenous clindamycin and imipenem. The kidneys showed evidence of obstruction of the collecting ducts by myeloma protein but there was no evidence of amyloidosis or glomerular pathology. The cause of death was attributed to acute Staphylococcal infection.
which was deemed an unavoidable complication of the requirement to actively treat her renal failure.

Discussion

Malignant multiple myeloma (MM) is a disease which predominantly affects the middle-aged and elderly. In the earlier description, we report the case of a 32-year-old female who presented with MM in the post-partum period, having previously been diagnosed with MGUS. Progression of her MGUS had been noted prior to her pregnancy although at this time there was no evidence of the development of myeloma. Her paraprotein and renal function remained stable during her pregnancy. However, 3 months following delivery she presented with acute renal failure secondary to the presumed myeloma kidney and despite appropriate management; she died from Staphylococcal septicaemia as a complication of her treatment.

The incidence of myeloma complicating pregnancy is very low but has been reported previously. To our knowledge there are nine previous case reports of myeloma diagnosed during pregnancy or in the postpartum period in patients ageing from 27 to 41 years [2–10]. None of these cases developed renal failure requiring renal replacement therapy. Furthermore, none of these cases had been documented to have MGUS prior to diagnosis of myeloma. In this particular case, we suggest that the physiological changes of pregnancy may have contributed to the progression of MGUS to MM.

The rate of progression of MGUS to MM is ~1% per year [1]. Progression of MGUS to MM is generally considered to be a multi-step process involving the accumulation of oncogenic mutations, although the factors contributing to disease progression are incompletely understood [11]. It is possible that the physiological adaptations associated with pregnancy could impact on the progression of MGUS/MM. The serum levels of two well-characterized growth factors for MM cells, interleukin-6 (IL-6) [12,13] and insulin-like growth factor 1 (IGF-1) [14], are increased during pregnancy [11,15]. The effect of oestrogen or progesterone on the progression of MGUS/MM is unclear, however a significant proportion of human myeloma-derived cell lines have been demonstrated to express either the oestrogen or progesterone receptor [16]. In vitro, addition of a selective oestrogen receptor modulator reduced the proliferation of human myeloma-derived cell lines. Addition of anti-oestrogens also impaired the growth of myeloma-derived cell lines as well as inducing apoptosis of myeloma cells [17]. Taken together, these observations suggest that pregnancy may increase the availability of growth factors for MM cells.

The immunological implications of viviparity may impact on the maternal immune response to MM cells. Implantation of fetal tissue into the uterus is habitually tolerated by the maternal immune system, despite the expression of allogeneic paternal-derived major histocompatibility complex molecules.

In addition, recent evidence suggests an important role for regulatory T cells (Treg) in the regulation of immune responses towards fetal antigens. Treg play a critical role in maintaining peripheral tolerance to self antigens [18] and have also been demonstrated to suppress immune responses to alloantigens in transplantation [19] and tumour-associated antigens [20].

In summary, there is evidence of both local and systemic adaptations during pregnancy that allow the temporary down-regulation of immune responses directed at paternal antigens expressed on fetal tissue raising the possibility that cross-reactivity between paternal antigens and altered maternal antigens on malignant cells could lead to temporary impairment of immune surveillance during pregnancy. In addition, increased levels of IL-6 and IGF-1 could facilitate the outgrowth of a malignant plasma cell clone.

Conflict of interest statement. None declared.

References

13. Amourdruz P, Minang JT, Sundstrom Y et al. Pregnancy, but not the allergic status, influences spontaneous and induced interleukin-1beta (IL-1beta), IL-6, IL-10 and IL-12 responses. Immunology 2006; 119: 18–26
14. Gargosky SE, Moyse KJ, Walton PE et al. Circulating levels of insulin-like growth factors increase and


Received for publication: 17.2.07
Accepted in revised form: 13.4.07