Case Report

Microscopic polyangiitis: first report of a case with onset during pregnancy

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Introduction

We report the case of a 24 week primagravida with a 20 year history of type 1 diabetes, presenting with microscopic polyangiitis manifesting as a renal-pulmonary syndrome. She required 13 days ventilation and was immunsuppressed with cyclophosphamide, steroids and plasmapheresis. The patient made a full recovery and delivered a healthy girl at 35 weeks gestation. This is the first reported case of MPA defined by the Chapel Hill Consensus (CHC) criteria presenting in pregnancy. We review the literature on systemic vasculitis and immunosuppressive therapy in the puerperium.

Case

A 25-year-old primagravida presented at 24 weeks gestation with a 1 week history of dyspnoea and a 2 day history of frank haemoptysis. There were no upper respiratory tract symptoms, no history of chest pain and no family history of thromboembolic disease. Past medical history included type 1 diabetes diagnosed at the age of 6 years: she had background retinopathy and proteinuria. Her only medication on admission was insulin. She was a non-smoker. The patient’s father had died 1 year previously from a myocardial infarct, shortly after presenting with renal failure secondary to rapidly progressive glomerulonephritis (RPGN). On examination, the patient was comfortable at rest and was able to speak in full sentences. She was clinically euvoalaemic, apyrexial and had a pulse rate of 120/min and a blood pressure of 130/80. Oxygen saturation was 94% on air. There was no clinical evidence of a deep vein thrombosis. Initial investigations revealed; creatinine 76 μmol/l, urea 3.1 mmol/l, potassium 4 mmol/l, Hb 8.9 g/dl (11.5–16.4), WBC 16.5 × 10⁹/l, platelets 522 × 10⁹/l, HbA1C 6.6%. Bone chemistry, coagulation screen and liver biochemistry were normal. Her chest radiograph showed bilateral lower zone consolidation (Figure 1). Urinalysis was positive for blood and protein (1.83 g protein/24 h). Blood and urine cultures were negative. A clinical diagnosis of pulmonary haemorrhage was made. Confirmatory pulmonary function tests were not completed as the patient’s condition deteriorated rapidly and she was transferred to the intensive care unit for respiratory support. A diagnostic renal biopsy was obtained 3 days after admission and contained 20 glomeruli. Light microscopy demonstrated seven glomeruli with a focal segmental necrotizing glomerulonephritis and three glomeruli with crescents (Figure 2A). There were additional changes consistent with a mild diffuse diabetic glomerulopathy. Immunohistochemistry demonstrated linear IgG staining of the basement membrane (Figure 2B). Immune serology was negative for antiglomerular basement membrane [GBM (quantitative ELISA, Pharmacia, Catalogue no. 133 96)] antibodies and anti-nuclear antibodies [ANA (qualitative assay using HEp-2 cells)] but was positive for anti-neutrophil cytoplasmic antibodies with a perinuclear pattern on immunofluorescence [pANCA (qualitative assay using neutrophils)]. Myeloperoxidase (MPO) specificity was confirmed by quantitative ELISA (The Binding Site limited, product code MK031) at a concentration of 34 units/ml (0–9 units/ml).

The patient received 10, 3 dm³, plasma exchanges (HAS 4.5%, 2.5 dm³ and FFP, 0.5 dm³), 1 g i.v. cyclophosphamide and 1 g daily i.v. methylprednisolone, changed to 60 mg oral prednisolone after 3 days. She also received prophylactic co-trimoxazole and oral anti-fungal agents. She required 11 U of blood and was ventilated for a total of 13 days. The serum creatinine...
increased through the normal range from 54 μmol/l to a maximum of 136 μmol/l and then settled to a baseline of 90 μmol/l; renal replacement therapy was never required. The anti-MPO concentration reduced to 5.5 units/ml. The patient was discharged 17 days after admission. She received two further 1 g pulses of cyclophosphamide over the next 3 months and the prednisolone was reduced to 10 mg maintenance dose over 6 weeks, with monitoring of the pANCA titre, CRP concentration and clinical state. The co-trimoxazole was stopped 4 weeks before delivery because of the risk of neonatal neutropenia. Our patient was induced at 35 weeks gestation, 2 days after spontaneous membrane rupture. She received
two, 12 mg i.m. betamethasone injections pre-delivery to promote fetal lung maturation. She delivered, with Ventouse assistance, a girl weighing 1440 g (below the 0.4th centile). The mother is well 7 months post-partum and the baby is developing normally although postnatal investigations have demonstrated a single pelvic kidney.

**Discussion**

This is the first reported case of MPA, defined by CHC criteria, presenting in pregnancy. It illustrates the diagnostic dilemma of a rare cause of haemoptysis in pregnancy and adds to a small literature already available on systemic vasculitis and chemotherapy in the puerperium. It re-poses the question of the interactions between pregnancy and autoimmune disease.

Fresh haemoptysis in the third trimester of pregnancy is most commonly due to pulmonary emboli. A methodical approach to a potentially large differential diagnosis is essential to avoid missed diagnoses. The main clinical clues to the alternative diagnosis of a renal-pulmonary syndrome were; the indolent onset, positive urinalysis and diffuse rather than focal roentgenographic pulmonary changes. Our patient’s condition declared itself more aggressively before confirmatory pulmonary function tests were obtained. She was therefore treated empirically with plasma exchange and i.v. steroids before histology and supporting serology confirmed the diagnosis of MPA: cyclophosphamide therapy was then introduced. A necrotizing glomerulonephritis with crescent formation is consistent with a diagnosis of MPA notwithstanding the absence of demonstrable extraglomerular small vessel involvement. The absence of granulomata, non-involvement of the upper respiratory tract, pANCA positivity and anti-MPO specificity made a diagnosis of Wegener’s granulomatosis (WG) unsustainable. The linear binding of IgG to the GBM was due to diabetes mellitus. Co-existing Goodpasture’s/anti-GBM disease or systemic lupus erythematosus (SLE), both plausible alternative causes of a renal-pulmonary syndrome, were unlikely in view of negative anti-GBM and ANA serology. In addition, the focal and segmental distribution of necrosis and crescents is more typical of small vessel vasculitis whereas in Goodpasture’s/anti-GBM disease the glomerular lesions are typically diffuse and global. Salama *et al.* [1] discuss the rare presentation of Goodpasture’s disease with negative routine immune serology, emphasizing the importance of obtaining diagnostic histology in all cases. The patient’s family history of renal disease was only obtained later in the admission. Her father probably had idiopathic RPGN and anti-MPO by ELISA. In summary, the diagnosis of MPA in our patient was based on the clinical presentation of pulmonary haemorrhage, a necrotizing glomerulonephritis, positive MPO-ANCA and negative assays for anti-GBM antibodies and ANA.

Systemic small vessel vasculitis presenting in pregnancy is very rare and was first reported by Talbot *et al.* [2]. They describe WG presenting at 26 weeks gestation with delivery of a healthy 1000 g boy and full recovery by the mother with steroid and cyclophosphamide therapy. In current literature between 1970 and 2002, 21 cases of active WG are reported peri-puerperally in 18 patients. Wegener’s granulomatosis has been newly diagnosed in six pregnancies making a total of seven such cases of small vessel vasculitis including our patient [2,3]. Three new cases were diagnosed post-partum [4]. Relapse of WG during pregnancy may be more common. There have been 10 relapses of WG during pregnancy and two relapses postpartum [5]. We have re-classified three patients discussed in Auzary’s review [6]. First, Morton describes a case of hypersensitivity vasculitis, which has been mis-named as MPA but does not fit CHC criteria for this diagnosis and is therefore not included in our literature search [7]. Secondly, two cases described by Habib, had symptoms prior to pregnancy and are re-classified as relapses during pregnancy and post-partum, respectively, instead of new cases. Cetinkaya *et al.* [8] report a case of vasculitis in the second trimester with clinical, immunological and histological features consistent with a diagnosis of MPA. However, there are reasons to believe that this patient may have had a secondary vasculitis caused by sepsis. The patient presented with an unusually high fever and died, 18 days after starting immunosuppressive therapy, with MRSA septicaemia. No microbiological data at presentation, including blood culture results, are recorded and the patient did not have an echocardiogram to address the possibility of infective endocarditis. Curiously, no glomerular pathology is described and in the absence of more complete data, we have excluded this case.

The literature on polyarteritis nodosa (PAN) in pregnancy is confusing by definition according to the American Rheumatism Association 1990 criteria. These patients may meet either one of the different CHC criteria for the diagnosis of MPA or true PAN: this literature has not been separately reviewed for the purpose of this article.

Conventional treatment for small vessel vasculitis with pulmonary haemorrhage consists of steroids, cyclophosphamide and plasma exchange. Because of the severity of our patient’s disease, all three modalities were administered. In the absence of controlled clinical trials, plasma exchange may be the most important early treatment in such cases. In order to minimize the total dose of cyclophosphamide, it was given as monthly i.v. pulses with mesna cover. In most circumstances, azathioprine is substituted for cyclophosphamide after 3 months. After discussion with the patient, it was agreed to try and avoid further chemotherapy subject to monitoring to anticipate any disease relapse. Our patient’s disease remains controlled clinically and serologically on only oral prednisolone 10 mg daily, 28 weeks after initial presentation.

The risks of prednisolone and cyclophosphamide in relation to pregnancy have been reviewed previously...
and are listed in the Table 1. The consequences for future fertility with cyclophosphamide must be addressed before treatment. Pre-conception, the combined oral contraceptive pill may help preserve fertility. Females may have fertilized ova stored and some have used GnRH agonists to inhibit ovarian mitotic activity [9]. Pregnancy itself may help preserve fertility by inhibition of ovulation. The risk to fertility in females is less than in males to whom counselling and consideration for sperm storage should be offered.

There is no consensus on autoimmune disease activity in pregnancy (reviewed by Habib [5]). Although SLE activity may increase or decrease in pregnancy, attributed to an oestrogenic effect, there is no evidence that this holds for other small vessel vasculitides. The absence of a female preponderance in MPA and WG makes an oestrogenic association, at least theoretically, improbable [10]. In our review, 12 out of 22 cases were relapses and so patients with a prior diagnosis of small vessel vasculitis should be aware of the risks to future pregnancies. Nevertheless, a reporting bias is very likely and uncomplicated pregnancies in immunosuppressed patients are likely to be under-reported.

In summary, we report a unique presentation of MPA in pregnancy. A successful clinical outcome for mother and baby was achieved with aggressive conventional immunosuppression.

Conflict of interest statement. None declared.

References


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