CASE REPORT

Isolated folate deficiency causing profound pancytopenia in pregnancy

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SUMMARY

New-onset pancytopenia in pregnancy is challenging in the clinical setting particularly as the management and outcome of pregnancy are entirely dependent on the underlying aetiology. In the absence of increased peripheral destruction, for example, hypersplenism, bone marrow (BM) failure should be considered as the cause of pancytopenia. Profound folate or B₁₂ deficiency may result in BM failure and are relatively easy to diagnose and manage. Other causes include aplastic anaemia (AA), infiltration by a haematological malignancy and other non-haematological disorders. We report a 26-year-old woman presenting with severe pancytopenia due to folate deficiency with complete recovery observed after folic acid replacement. This case highlights the importance of recognising folate deficiency as a reversible cause of pancytopenia, since prompt replacement can lead to rapid normalisation of counts with no subsequent clinical sequelae. We also consider the indications for measuring serum folate in pregnancy.

BACKGROUND

Severe folate deficiency can cause megaloblastic anaemia and pancytopenia. It is most often observed in cases of poor diet such as those deficient in legumes, chronic alcoholism and certain gastrointestinal diseases.¹ Its incidence in pregnancy has been reported to be as low as 0.2%, however this may increase to 30% depending on geographical, social and economic status.² Despite the increased folate requirements associated with pregnancy, serum levels are not routinely measured. Folate supplementation however is recommended preconception to reduce the risk of neural tube defects.³ Here we review a case of folate deficiency in pregnancy with a severe pancytopenia akin to acute leukaemia. The contributory factors are subsequently discussed since despite its rarity in the Western world, an awareness of the risk factors for its development is important for the prevention of an adverse outcome in pregnancy.

CASE PRESENTATION

A 26-year-old woman (gravida 4, para 3) was admitted at 31 weeks gestation with worsening fatigue and shortness of breath on exertion over a duration of 1 month. More recently, she had noticed occasional gum bleeding and easy bruising. At 11 weeks gestation she had been treated with intravenous fluids for viral gastroenteritis, the symptoms of which resolved within a few days. She reported that her appetite had never fully recovered but had attributed this to pregnancy-related nausea. She denied any fever, night sweats or itching. There was no history of

alcohol excess or any dietary restriction. She had no medical or family history of note. All her previous pregnancies had been uneventful.

On examination, she was pale with few petechiae seen on the buccal mucosa. Her blood pressure was 120/80 mm Hg with a trace of protein detected on urine dipstick. There was no lymphadenopathy or splenomegaly palpable. The remainder of the clinical examination was unremarkable. An ultrasound confirmed normal fetal movement and development for gestation.

INVESTIGATIONS

A full blood count revealed a macrocytosis with a severe pancytopenia; haemoglobin of 72 g/L (115–165 g/L) with a mean cellular volume of 104 fL (80–100 fL), platelets $15 \times 10^9/L$ ($150\text{--}400 \times 10^9/L$) and neutrophils $0.5 \times 10^9/L$ ($1.7\text{--}7.5 \times 10^9/L$). Her last recorded haematological profile 5 months ago was within normal limits. Reticulocyte count was $8 \times 10^9/L$ ($20\text{--}80 \times 10^9/L$) and renal function, liver function tests and coagulation screen were normal. A blood film showed red cell variation with macrocytes present and no significant red cell fragmentation. Right shifted neutrophils and thrombocytopenia were seen with no immature precursors. Ferritin was normal and vitamin B₁₂ level was 199 pg/mL (191–663 pg/mL), however serum folate was subtherapeutic at 2.7 ng/mL (4.6–18.7 ng/mL). An autoimmune screen was unremarkable. Antitransglutaminase antibodies were negative.

An urgent bone marrow (BM) was carried out to exclude a neoplastic process. The aspirate was hypercellular with megaloblastoid features. Early erythroid precursors and giant metamyelocytes were seen (figure 1) however, no leukaemic population was found on microscopy or immunophenotyping. Karyotype analysis revealed normal XX karyotype.

TREATMENT

She was transfused with two units packed red cells and one adult dose of platelets. She was then started on folic acid 5 mg daily. A single dose of 1 mg hydroxycobalamin was also administered. Five days later, the neutrophil count had recovered ($1.4 \times 10^9/L$) with an increase in platelet count ($25 \times 10^9/L$; figure 2).

OUTCOME AND FOLLOW-UP

Her counts continued to normalise on follow-up with no further blood product support. She gave birth to a healthy male baby 7 weeks later weighing 6 pounds, 13 ounces. His full blood count was normal and there were no signs of neurological compromise.

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Figure 1 (A) The aspirate smear demonstrated erythroid precursors with megaloblastoid features, a relative reduction in myeloid activity with a degree of maturation arrest and giant metamyelocytes ($\times 60$ magnification). (B) Black arrow, megaloblastic erythroid precursor, green arrow, giant metamyelocyte ($\times 100$ magnification).

DISCUSSION

Folate deficiency is a cause of macrocytosis in pregnancy. Left untreated, it could progress to severe megaloblastic anaemia

Figure 2 Count recovery with time (days).

with pancytopenia. Peripheral blood film may reveal macrocytic anaemia and hyper-segmented neutrophils with varying degree of leucopenia and thrombocytopenia. BM examination could demonstrate megaloblastic changes reflecting ineffective haematopoiesis and resultant BM failure.¹ In the Western world, this is a rare occurrence with other serious, haematological conditions being more prevalent. Indeed BM failure due to aplastic anaemia (AA) was originally described in a pregnant woman and there have been subsequent reports describing this association.⁴ In a recent review of 24 pregnancies with new-onset cytopenias, over half were diagnosed with AA followed by myelodysplasia—a preleukaemic condition—occurring in 25%. Megaloblastic anaemia due to folate or B_{12} deficiency was observed infrequently.⁵

In the majority of developed countries, folic acid supplementation (at least $400 \mu g$) is recommended for 2–3 months prior to conception and throughout pregnancy into the post-partum period.⁶ This been adopted as a worldwide strategy to reduce the incidence of fetal neural tube defects (NTD) such as anencephaly, spina bifida and meningomyelocele. This has been estimated to reduce the incidence NTD by 70%.^{1 3} Its protection may also lower the risk of other congenital anomalies and adverse pregnancy outcomes including spontaneous abortions, placental abruption and low birth weight.⁷ In a recent observational study evaluating the effect of folic acid supplementation against adverse pregnancy outcomes other than NTD, the rates of pre-eclampsia and small for gestational age were reduced compared to the control group.⁶

Folate deficiency is most often a result of poor dietary intake either alone or in combination with malabsorption or increased utilisation. Excess cell turnover may be physiological such as in pregnancy and lactation or pathological such as in haemolysis or chronic inflammatory disorders. Other causes of folate deficiency include excess urinary loss (liver or cardiac failure), drugs (anticonvulsants), long-term dialysis and alcoholism. An average adult daily Western diet contains $200\text{--}250 \mu g$ with a minimum daily requirement of $100\text{--}150 \mu g$ which may increase to $600 \mu g$ in pregnancy. Total adult body stores are $10\text{--}12 \text{ mg}$ and are only sufficient for approximately 4 months, so severe folate deficiency can occur rapidly.¹

It is usual to assay serum B_{12} and folate concurrently due to their requirement in the production of deoxyribonuclease synthase. Unlike serum folate, vitamin B_{12} levels fall by 30% in the third trimester and are less reliable in determining true deficiency.⁸ In addition, folate deficiency can also lead to low/sub-normal serum B_{12} levels due to overutilisation of B_{12} in the absence of folate. In this scenario, measurement of the plasma binding protein transcobalamin rather than B_{12} may be more meaningful.

Other biomarkers such as homocysteine (Hcy) have been utilised in diagnosing megaloblastic anaemia, with elevated Hcy levels correlating with a deficiency of B_{12} or folate. Hcy is a recognised risk factor of cardiovascular disease with reports of a protective benefit conferred by vitamin replacement therapy.⁹ It is not, however a specific marker of folate deficiency and there are a number of factors influencing total plasma Hcy levels including age, gender, medications, diet, other nutritional vitamin deficiencies and renal function. Furthermore, the requirements in terms of sample timing and technical analysis are stringent. Therefore, in cases such as ours where the diagnosis of folate deficiency is clear, current guidelines do not suggest the routine testing of plasma Hcy levels.¹⁰ Our patient did not have measurement of plasma Hcy level.

While there is no requirement to measure serum folate routinely in pregnancy, testing should be sought in those with a history of poor or inadequate diet, any symptoms of malabsorption and those with an unexplained macrocytic anaemia. Hyperemesis during pregnancy and multiparity are also recognised as risk factors prompting investigation.¹⁰ We propose that any intercurrent gastrointestinal illness in pregnancy should also heighten suspicion as observed in this case.

Folic acid deficiency causing severe BM failure is an infrequent but possible clinical scenario in pregnancy which can be reversible following diagnosis and treatment. The importance of a detailed history for the relevant risk factors cannot be over emphasised.

Learning points

- ▶ Severe pancytopenia due to folate deficiency during pregnancy may mimic other causes of bone marrow (BM) failure such as aplastic anaemia or bone marrow replacement by haematological and non-haematological disorders.
- ▶ While BM investigation is a key diagnostic tool, risk factors for folate deficiency—including a history of intercurrent gastrointestinal illness—should be sought in the event of an unexplained anaemia and/or macrocytosis.
- ▶ Prompt treatment with folic acid can lead to a reversible haematological profile and favourable pregnancy outcome.

Competing interests None.

Patient consent Obtained.

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