Chronic histiocytic intervillositis (CHI): an under-recognised condition with potential serious sequelae in pregnancy

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SUMMARY

Chronic histiocytic intervillositis (CHI) is a rare placental disorder associated with adverse pregnancy outcomes and high recurrence rates in subsequent pregnancies. We discuss a case of CHI diagnosed incidentally in a young primigravida who presented with a first trimester miscarriage. CHI is usually diagnosed after an adverse pregnancy outcome by microscopic placental histopathology. Currently, CHI is a poorly understood condition by clinicians in many aspects, including its aetiology and subsequent management of patients in their future pregnancies. This is due to the lack of awareness and underdiagnosis of CHI among general pathologists and obstetricians. The authors would like to highlight this interesting case to encourage more research on CHI to understand its pathophysiology and optimal management better. Clinicians should also focus on providing holistic care to this group of patients by considering the impact of adverse pregnancy outcomes on their emotional well-being.

BACKGROUND

Early pregnancy miscarriages are common and occur in up to 20% of clinical pregnancies.[1] Approximately 80% of early pregnancy losses occur in the first trimester and half of them are attributed to fetal aneuploidy. Advanced maternal age and previous early miscarriages are risk factors for early pregnancy losses. The risk of miscarriage in women aged 20–30 years is 9%–17% and rises exponentially to 40% at 40 years and 80% at 45 years of age.[2]

Chronic histiocytic intervillositis (CHI), otherwise known as massive perivillous histiocytosis, massive chronic intervillositis or chronic intervillositis of unknown aetiology,[3] is a rare placental disorder where there is significant infiltration of the placental intervillous space by maternal histiocytes and occasional lymphocytes. The incidence of CHI is often under-reported. It is estimated to be highest in the first trimester, between 4.4 and 9.6 in 1000 miscarriages.[4–6] In comparison, only 0.6 in 1000 cases are diagnosed in the second and third trimesters.[4–6] A high recurrence rate of 70%–100% is reported in subsequent pregnancies.[7]

We discuss a case of CHI diagnosed on histopathology of products of conception (POC) in a young primigravida who presented to KK Women's and Children's Hospital (KKH) with an early miscarriage. KKH is the largest tertiary referral centre for obstetrics in Singapore and has the support of perinatal pathologists.

CASE PRESENTATION

A 25-year-old primigravida was booked for routine antenatal care at 5 weeks and 3 days of gestation. She denied any abdominal pain or per-vaginal bleeding and reported having regular menstrual periods. She had no significant medical or family history of hypertension or autoimmune disorders. This was a spontaneous planned pregnancy from a non-consanguineous marriage. She conceived within the first cycle of trying. She was a non-smoker, non-drinker and had no drug allergies. She had no recent travel history to malaria-endemic regions.

There were no abnormalities noted on physical examination. She was of a normal body mass index at 22.6. Her vitals were stable with a blood pressure of 124/79 mm Hg and heart rate of 82 beats/min. Urine dipstick was negative for protein and glucose.

A transvaginal ultrasound scan performed confirmed a viable intrauterine pregnancy with a crown rump length (CRL) of 3 mm that corresponded to 5 weeks and 5 days of gestation. She presented 2 weeks later with vaginal spotting. A repeat transvaginal scan done showed a non-viable pregnancy with a CRL of 8 mm which corresponded to 6 weeks and 6 days of gestation. A diagnosis of a missed miscarriage was made. The patient opted for conservative management.

She presented 4 days later with significant abdominal pain and vaginal bleeding associated with spontaneous expulsion of the POC at home. Physical examination and a transvaginal scan confirmed the diagnosis of a complete miscarriage. She requested for the POC to be sent for histopathology as she wanted to determine the cause of her miscarriage.

INVESTIGATIONS

Histopathological findings of the POC showed a small amount of avascular chorionic villi with a prominent amount of intervillous fibrin deposition admixed with CD68 positive histiocytes. The features were suggestive of CHI. There was no gestational trophoblastic disease or malignancy seen.

Following the diagnosis of CHI, an opinion from a maternal–fetal specialist was sought. A referral to rheumatology was recommended. Autoimmune conditions including systemic lupus erythematosus and antiphospholipid syndrome were excluded.

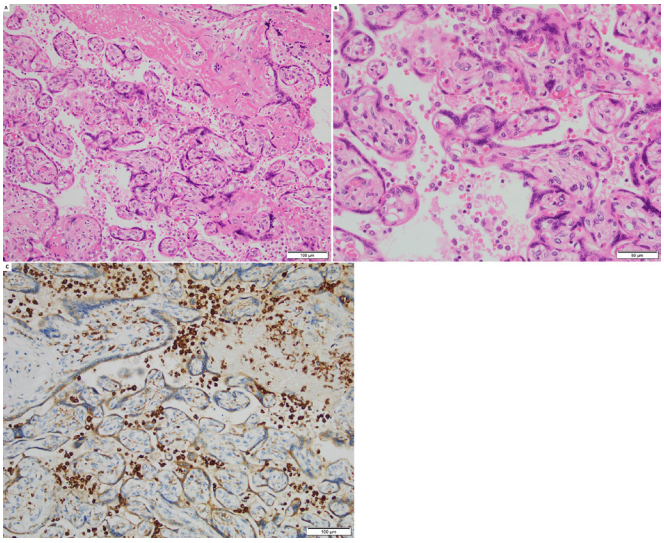

Figure 1 Chronic histiocytic intervillositis seen in central placental disc sections from a 31-year-old woman with an infant delivered at 36 weeks. (A) Histology shows prominent intervillous mononuclear histiocytes with increased fibrin deposition between villi (200× magnification, H&E). (B) High-powered photomicrograph showing mononuclear histiocytes in the intervillous spaces (400× magnification, H&E). (C) CD68 immunostaining confirms CD68 positive histiocytes in the intervillous spaces (400× magnification).

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of CHI from a histopathological point of view include chronic villitis, which can be of infectious origin or of unknown aetiology.[7] These are characterised by a predominantly intervillous lymphohistiocytic infiltrate.[8] The other differentials include massive perivillous fibrin deposition or maternal floor infarct.[7] The predominant histopathological feature is significant fibrinoid deposition in the perivillous space.[7] Infections which present with a prominent intervillositis feature include malaria, listeria, tularaemia and coccidioidomycosis.[4 5]

Box 1 Key counselling points for patients with chronic histiocytic intervillositis (CHI)

1. CHI is a rare and serious placental disorder that affects less than 1% of pregnancies.[4–6]
2. It is diagnosed retrospectively through histopathology, most commonly following an adverse pregnancy outcome.[7 10]
3. It affects all trimesters, most commonly in first trimester miscarriages.[5]
4. Associated with adverse pregnancy outcomes, including recurrent miscarriages, intrauterine growth restriction (IUGR), preterm births and intrauterine deaths.[5 9 10]
5. Associated with high recurrence rates of 70%–100%.[7]
6. No definite association of CHI with patient demographics or serum biomarkers.[11]
7. CHI is currently under-reported. It should be considered in patients with recurrent pregnancy losses, previous CHI on histopathology, those with poor obstetric outcomes (IUGR, pre-eclampsia and unexplained stillbirths) and a history of hypertension or autoimmune disorders.
8. No established management guidelines currently. However, some prospective studies have shown benefit of empirical antenatal treatment with aspirin, low-molecular-weight heparin, prednisolone and hydroxychloroquine.[3 9 10]
9. Any subsequent pregnancy should be managed as a high-risk pregnancy with multidisciplinary team care.

TREATMENT

She was managed conservatively for her missed miscarriage initially, following which she had a complete miscarriage.

OUTCOME AND FOLLOW-UP

During her subsequent follow-up, she reported that she had recovered well and had spontaneous return of her menses 1 month following the miscarriage. She was physically and emotionally well and has plans to conceive soon.

Currently, there are no clinical guidelines on the management of CHI. This poses a management dilemma for our patient in her subsequent pregnancies. She will be managed as a high-risk pregnancy with multidisciplinary team care in the obstetric high-risk clinic in our institution. She was advised to book early for her next pregnancy for consideration of empirical therapy (aspirin, low-molecular-weight heparin (LMWH), prednisolone or hydroxychloroquine) to improve her pregnancy outcome.

DISCUSSION

CHI, a rare placental disorder, has been reported to be associated with adverse maternal and fetal outcomes. Recurrence rates of 70%–100% have been reported in subsequent pregnancies.[7] Adverse pregnancy outcomes include early and late miscarriages, intrauterine growth restriction (IUGR), preterm birth and intrauterine death (IUD).[5 9 10] A higher risk of pre-eclampsia has been reported at 9.9% in patients with CHI as compared with 1.8% in those without.[10] Pregnancy losses can occur at any gestation, most commonly in the first trimester. Statistics for these outcomes vary significantly between studies. In a retrospective study of 69 patients with CHI conducted by Marchaudon *et al*, 30.4% had early miscarriages, 13% had late miscarriages, 61.5% had IUGR and 26.1% ended in IUD.[5] Only 30.4% had live births and 75% of these births were preterm.[5] Boyd and Redline reported a perinatal mortality of 77% with only 18% of pregnancies reaching term in their case series.[4]

The aetiology for CHI is currently unknown. It is believed to be an immunological process involving maternal T lymphocytes responding to foreign paternal antigens during pregnancy.[4] Several studies have proposed a potential association of CHI with medical conditions like autoimmune disease and hypertensive disorders. It has been reported that 18.2% had hypertensive disorders while 6%–58% had autoimmune conditions.[11] However, our patient did not have these medical conditions.

The definitive diagnosis of CHI is confirmed by microscopic histopathology of the POC or placenta.

Bos *et al* proposed a standardised pathological criteria for diagnosing CHI[12] :

1. A predominantly mononuclear infiltrate must be present in the intervillous space (figure 1A,B).
2. Approximately 80% of the mononuclear cells in the intervillous space must be CD68 positive (figure 1C).
3. ≥5% of the intervillous space must be occupied by the mononuclear infiltrate.
4. Clinical or histopathological signs of infection should be excluded.

Positive CD68 immunostaining has been reported to be useful in the diagnosis of CHI (figure 1C), especially for non-perinatal pathologists who may be less familiar with this condition.[13]

As per international guidelines, obstetricians do not routinely investigate after one miscarriage. Investigations are usually performed in patients with two or more miscarriages. However, some propose that histological analysis of POC obtained either from spontaneous passage, medical or surgical methods should be conducted to exclude other pregnancy complications such as ectopic pregnancy, gestational trophoblastic disease or to identify incomplete miscarriage.[1] Others propose that histological examination does not always accurately detect the aforementioned pathologies and cannot confirm successful termination of pregnancy.[14]

However, clinical features that might prompt clinicians to send POC for histopathology following one miscarriage include uncertainty of diagnosis, obtaining a smaller than expected amount of POC or suspected trophoblastic tissue collected during uterine evacuation.[1 14] Based on current evidence, there are no defined patient demographics that warrant investigations for CHI. With the increasing awareness of CHI, we suggest that patients with the following risk factors should be considered for histopathological examination of the POC or placenta in view of their higher risk of CHI:

1. Patients with recurrent pregnancy losses.
2. Previous CHI on histopathology.
3. Previous poor obstetric outcomes (IUGR, pre-eclampsia, unexplained stillbirths).
4. History of hypertension or autoimmune conditions.

Some studies have shown that there are biochemical and radiological findings associated with CHI.

Elevated serum alkaline phosphatase (ALP) has been reported in patients with CHI,[5 10 11 15] but its association with adverse fetal outcomes is debatable. Koby *et al* concluded that raised ALP was not associated with severe fetal morbidity,[11] while Marchaudon *et al* report that 80% of women with very high ALP levels had babies with IUGR.[5] Some authors have identified an association of first and second trimester fetal aneuploidy serum biomarkers such as pregnancy-associated plasma protein-A, beta-human chorionic gonadotrophin, inhibin-A and alpha-fetoprotein with CHI and adverse pregnancy outcomes.[11] Further multicentre studies should be performed to ascertain these biomarkers' association with CHI and its use for risk stratification.

Several ultrasound findings have been reported in patients with CHI.[10 11] It was found that 40% of cases with CHI had abnormal placental dimensions (length <10 cm or width >4 cm) while 35% had abnormal uterine artery Doppler in the initial mid-trimester scans.[11] Subsequent scans showed that 72% had abnormal umbilical artery Doppler, 44% had abnormal placental morphology (abnormal echotexture, cystic lesions) and 40% had oligohydramnios.[11]

There have been studies delineating empirical treatments at the point of our publication, including antiplatelet, immunosuppressive and anticoagulant drugs, with some reported success. These include monotherapy with aspirin, LMWH or corticosteroids and combination therapy, including a mixture of aspirin, LMWH, corticosteroids and hydroxychloroquine.[3 9 10] However, the efficacy of these treatments has yet to be proven. They are used due to the possible underlying immunological aetiology of CHI.[4] Patients with more complicated medical and obstetric histories were more likely to receive combination therapy.[9]

Mekinian *et al* conducted a multicentre prospective study of 24 pregnant patients with a history of CHI.[9] They were allocated into untreated and treated groups. Within the treatment groups, they were further divided into subgroups that received monotherapy or combination therapy. There was an increase in live birth rate from 32% to 67% in the treated group.[9] However, the risk of preterm delivery and recurrence of pregnancy complications remained the same despite intervention.[9]

D'Souza *et al* have recently proposed an algorithm for the antenatal management of subsequent pregnancies following a diagnosis of CHI, with details to be delineated in an upcoming publication.[16] More prospective, multicentre studies will be required to better understand CHI and its management.

As clinicians, we often focus on the clinical management of patients and may neglect the impact of a miscarriage on patients and their loved ones. However, women do experience a myriad of emotions following a miscarriage. 40% of women report grief, and the time taken for resolution of symptoms varies from 3 months to 2 years.[17] 10% to 55% of women are diagnosed with major depressive disorders (MDDs) after a miscarriage.[17] They tend to be symptomatic for 6 months before returning to baseline after a year. 20% to 40% experience anxiety soon after the miscarriage.[17] The time taken for women to recover from anxiety is similar to those with MDD.

Having a history of miscarriage also influences women's experiences in their subsequent pregnancies. They tend to be more alert and cautious about potential risks in pregnancy and may experience anxiety, depression and even post-traumatic stress disorder.[18] This emotional stress would be more pronounced in our patient given the diagnosis of CHI. Therefore, it is pertinent to address the impact of this diagnosis on her psychological well-being by managing her with extreme compassion and sensitivity.

The authors hope that this case report will increase awareness among obstetricians and pathologists regarding CHI and its adverse implications. Key counselling points for patients with CHI for obstetricians can be found in box 1.

Learning points

- Chronic histiocytic intervillositis (CHI) is a rare and serious placental condition. It is currently under-recognised. Obstetricians should consider CHI in the differential diagnosis in all patients with adverse pregnancy outcomes. Awareness of this placental disorder through histopathology can be considered to diagnose this rare entity.
- CHI is associated with adverse pregnancy outcomes and high recurrence rates.
- The optimal management for CHI is currently not available in international guidelines. We hope that more multicentre studies will be performed to ascertain the optimal treatment for CHI.
- Typically, clinicians investigate after a second or third miscarriage. Histopathological analysis of products of conception is not widely performed for patients following one miscarriage. However, this can be considered for some patients as miscarriages often have a significant impact on patients' emotional and mental well-being.

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