

Chronic histiocytic intervillitis in three consecutive pregnancies in a single patient: Differing clinical results and pathology according to treatment used

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Abstract

Chronic histiocytic intervillitis (CHI) is an extremely rare pathological condition but is strongly associated with severe obstetric complications and has a high recurrence rate. The management of this condition has not yet been established. We describe herein the occurrence of CHI in the late second–third trimester in each of three consecutive pregnancies in a single patient with four previous consecutive early miscarriages. In this patient, each of the three complicated pregnancies was managed with one of the following, respectively: low-dose aspirin; heparin plus low-dose aspirin; and prednisolone plus low-dose aspirin. CHI was histologically confirmed in all three pregnancies, but the clinical results and pathology (e.g. extent of histiocytic infiltration) in each pregnancy clearly differed with treatment. Both combination treatments eventuated in a live birth. Immunosuppressive therapy seemed to produce better clinical results by restricting the extent of the affected areas. The elevated alkaline phosphatase associated with the CHI was assumed to have no clinical prognostic value.

Key words: anticoagulant, chronic histiocytic intervillitis, fibrin deposition, prednisolone, recurrent pregnancy loss.

Introduction

Chronic histiocytic intervillitis (CHI) is a rare placental lesion characterized by marked infiltration of maternal mononuclear inflammatory cells into the intervillous space, which can be accompanied by varying intervillous fibrin deposition.^{1–5} The incidence of CHI is reportedly 4.4% in first trimester miscarriages with a normal karyotype,⁴ and quite rare in the second or third trimester (0.6 in 1000).⁵ The condition is strongly associated with highly recurrent, severe obstetric complications including spontaneous abortion, fetal growth restriction (FGR), and intrauterine fetal death (IUFD).^{1–9} The etiology of CHI remains unclear but the

aberrant recruitment of maternal immune cells to the maternal–fetal interface suggests an anomalous maternal immunological response to fetal tissue.^{1–5,10,11} Use of anticoagulant and immunosuppressants to prevent recurrence in subsequent pregnancies has been anecdotally reported but their efficacy is dubious.⁷

The present patient had CHI in each of three consecutive pregnancies during the late second or third trimester following recurrent first trimester miscarriages. The three pregnancies were managed with different treatments. While each produced disparate clinical and pathological results, the combination of prednisolone and low-dose aspirin (LDA) had the most favorable obstetric outcome.

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Case Report

A 29-year-old woman was referred to the perinatal center for recurrent pregnancy losses (RPL) including four consecutive early miscarriages (one biochemical pregnancy loss, two anembryonic losses, and one embryonic loss) followed by one stillbirth at 27 weeks. The histology for the four early miscarriages was not available. The fifth pregnancy was managed with LDA (81 mg/day) but fetal growth was retarded at 15 weeks (biparietal diameter [BPD], 24.5 mm; -2.5 SD) and arrested at 17 weeks. Severe oligohydramnios was also observed. A female stillborn infant weighing 210 g with no surface anomaly was delivered. The pathology report from the previous hospital noted that the placenta, weighing 125 g, had a broad infarction with inflammatory cell infiltration and also noted the presence of a single umbilical cord. We performed detailed examinations for RPL but failed to find any possible causes such as antiphospholipid antibodies. The past and family medical histories were unremarkable.

The sixth pregnancy was achieved by induced ovulation at age 31 years. Anticoagulant therapy was started with LDA (81 mg/day) and heparin injections (10 000 IU/day) at 4 weeks of gestation. At 17 weeks ultrasonography indicated FGR (BPD, 32 mm; -1.8 SD) and a dappled mass (3–4 cm) on the fetal surface of the placenta (Fig. 1a). The patient was then hospitalized, and the heparin dosage was increased (15 000 IU/day). The placental mass enlarged, showing a homogeneous, echogenic pattern and was suspected to be a hematoma on magnetic resonance imaging at 20 weeks (Fig. 1b). After discontinuation of anticoagulant therapy, the mass acquired a heterogeneous appearance with the

shortening of activated partial thromboplastin time and a rise in coagulation markers. Severe FGR continued, and left uterine artery notching was noted on pulsed Doppler. The amniotic volume remained in the low normal range. At 33 weeks, cesarean section was performed due to non-reassuring fetal heart rate pattern following rupture of membrane.

A female infant weighing 1032 g (<3 rd percentile for gestational age) was delivered without any definite malformation. Interestingly, alkaline phosphatase

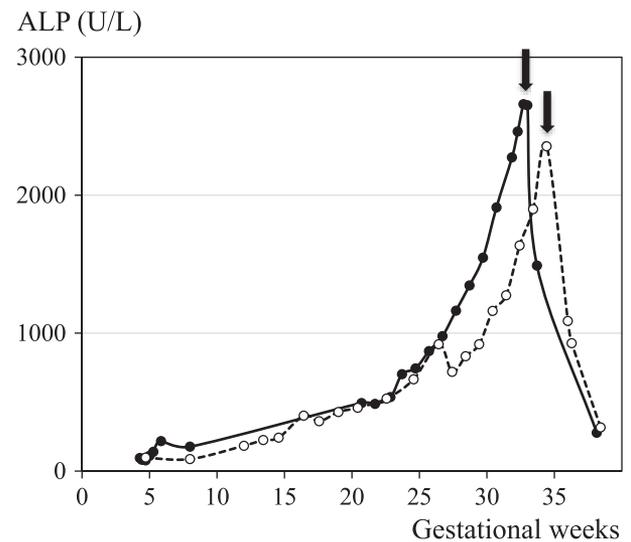


Figure 2 Change in serum alkaline phosphatase (ALP) during the (—●—) sixth and (- -○-) seventh pregnancies. Arrows, cesarean section. On isozyme analysis, increased ALP originated from the placenta in both pregnancies.

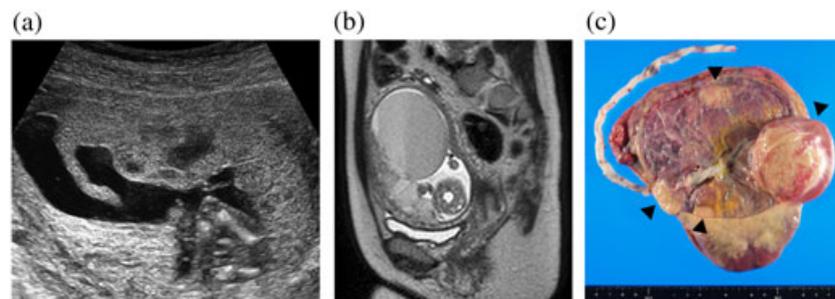


Figure 1 Placental mass detected in the sixth pregnancy. (a) Ultrasonography at 17 weeks. A dappled mass (3 × 4 cm) was observed on the fetal surface of the placenta near the placental shelf. (b) Sagittal T2-weighted magnetic resonance imaging at 20 weeks. On the fetal side of the placenta, a large mass was observed occupying the amniotic cavity (8.4 × 6.8 × 6.5 cm). The mass had a homogeneous pattern with a fluid–fluid level suggestive of hematoma. (c) Gross appearance of the placenta from the sixth pregnancy. On the fetal side, four nodules were observed (6 × 6, 3 × 1.5, 2.2 × 1.5, 2.2 × 1.5 cm; arrowheads) on the partial, markedly circumvallate placenta.

(ALP) dramatically increased from around 20 weeks and rapidly normalized after delivery (Fig. 2). The infant was removed from the neonatal intensive care unit on day 79 and then monitored at a local hospital. Delayed development and hypoplasia of the pontine and cerebellum resulting from *calcium/calmodulin-dependent serine protein kinase* (CASK) mutation were diagnosed at 1 year 5 months of age.¹² The placenta measured 16 × 13.5 × 1.5 cm and weighed 288 g. Macroscopically, there were several masses on the fetal surface of the placenta with partial, marked circumvallation (Fig. 1c). On microscopy these masses were seen to be the result of subchorionic fibrin deposition. No pathological evidence of cholangioma was seen. Marked infiltration of inflammatory cells, shown to be mostly histiocytes on CD68 immunostaining, was also noted throughout the intervillous space (Fig. 3b,c). Moderate intervillous fibrin deposition was also detected. This pathology corresponded to diffuse CHI.^{4,8} No evidence of chronic villitis or chorioamnionitis was seen. The slides of the placental sample from the fifth pregnancy

from the previous hospital were reviewed, and diffuse CHI co-occurring with moderate intervillous fibrin deposition was identified (Fig. 3a), indicating recurrence of diffuse CHI.

The seventh pregnancy was achieved naturally at age 36 years. Prednisolone 20 mg and LDA were prescribed at 4 weeks' gestation. ALP increased from around 20 weeks, as before (Fig. 2). At 26 weeks the patient was hospitalized, and continuous injections of β-stimulant were given for threatened premature delivery. Fetal growth remained within the low normal range despite the continuous presence of left uterine artery notching. Prednisolone was reduced by 2 mg per week from 29 weeks. At 35 weeks, a female infant weighing 2051 g (>10th percentile) was delivered by cesarean section due to labor onset following premature rupture of membrane. The placenta, measuring 16 × 12.5 × 2.5 cm and weighing 290 g, was normal macroscopically. Histologically, patchy, dense infiltration of inflammatory cells was noted (Fig. 3d), most of which were CD68 positive (data not shown). Compared with the previous

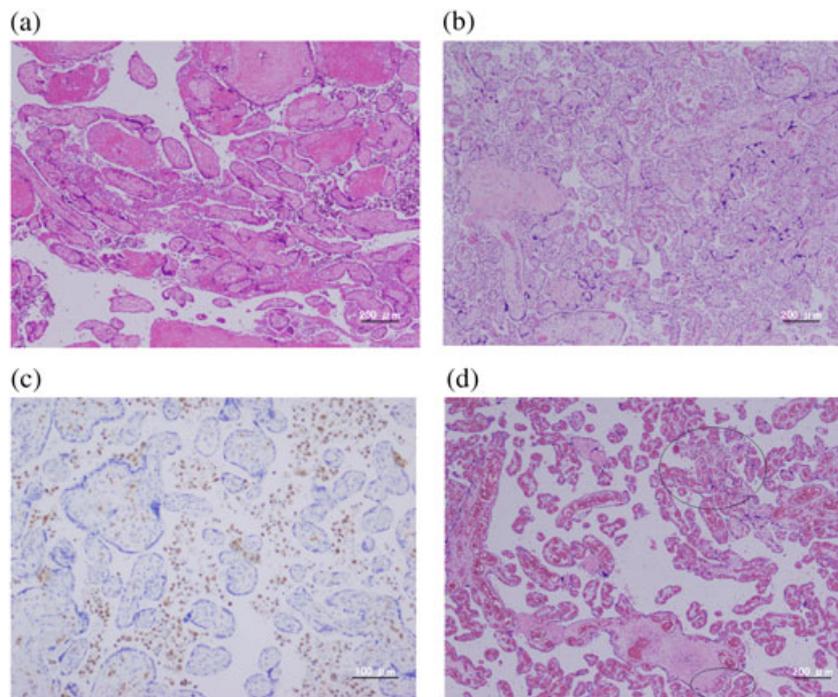


Figure 3 Pathology of the placenta during the (a) fifth, (b,c) sixth, and (d) seventh pregnancies. (a) Fifth pregnancy: the intervillous space was occupied by inflammatory cells in all the examined slides (diffuse chronic histiocytic intervillitis [CHI]). Fibrin deposition in the intervillous space was also noted (H&E; scale bar, 200 μm). (b) Sixth pregnancy: numerous mononuclear cells were observed in the intervillous space consistent with diffuse CHI (H&E; scale bar, 200 μm). (c) Sixth pregnancy: most inflammatory cells were immunoreactive for CD68, a monocyte/macrophage marker (scale bar, 100 μm). (d) Seventh pregnancy: patchy, dense CHI was observed (circles). The remaining regions were totally unaffected (focal CHI; H&E; scale bar, 200 μm).

pregnancies, the inflammatory area was clearly diminished, and the remaining regions were totally unaffected, suggesting focal CHI. "Focal" is used here to describe a heterogeneous, less extensive cellular infiltrate composed of mononuclear cells.^{4,8} Fibrin deposition in the subchorionic or intervillous space was also mild. Informed consent was obtained from the patient, and approval was obtained from the institutional ethics committee to publish these findings in a case report.

Discussion

Since first described by Labarrere and Mullen in 1987,¹ CHI has attracted a great deal of interest as a significant cause of recurrent, severe obstetric complications. A previous review article reported an FGR rate of 66.7% and an overall live birth rate of 53.6% in complicated pregnancies at the gestational age ≥ 14 weeks, and the pathological recurrence of CHI was confirmed in 80% of cases.⁷ In a prospective multicenter study, a prior history of FGR or IUFD and the histological persistence of CHI were associated with failure to have a live birth in subsequent pregnancies.⁹ The current evidence, however, is still insufficient to enable the drawing of conclusions as to the practical management of CHI, especially given that the efficacy of each treatment remains unclear. Reports of CHI occurring more than twice in a single patient are rare.^{3,6,7,10,13} The detailed clinical description of the present case provides useful information for managing and understanding CHI.

In this case, the heparin/LDA and prednisolone/LDA combinations led to a live birth in the sixth and seventh pregnancies, respectively, while the LDA monotherapy resulted in IUFD in the fifth pregnancy. A prospective study also indicated the need for combination therapy in the case of history of IUFD.⁹ In the present sixth pregnancy, the additional heparin treatment might have extended the gestational period despite the recurrence of diffuse CHI with early onset, severe FGR. Although the role of the *CASK* mutation was unclear, the diffuse CHI observed in the sixth pregnancy was very consistent with the cause of severe FGR. Interestingly, remarkable subchorionic fibrin deposition deriving from a massive hematoma was observed on the fetal side of the placenta in the sixth pregnancy. To the best of our knowledge, there are no reports on massive subchorionic hematoma in CHI. These masses may have been generated and aggravated by anticoagulant therapy rather than being associated with CHI.

In the seventh pregnancy better clinical results were obtained when the extent of the affected areas was restricted by replacing heparin with immunosuppressive therapy. Although the evidence remains limited, immunosuppressive treatments are thought to be effective because a maternal immunological dysfunction such as allogeneic humoral rejection is most likely the etiology of CHI.^{3,6,9-11,13} In five previously reported cases complicated by more than two occurrences of CHI, four patients successfully gave birth on prednisone or combined treatment including prednisone, but one patient had repeated, severe, early onset FGR despite receiving prednisolone plus LDA.^{3,6,7,10,13} In contrast, the CHI might become milder over time, in keeping with a spontaneous weakening of the autoimmune response itself,^{7,9} although in the present case the autoantibodies were all negative. This scenario, however, cannot fully explain the previously reported cases of CHI with miscarriage/stillbirth following live birth.^{3,6} The therapeutic efficacy of immunosuppression for the improvement of impaired maternal immunity requires further study.

Prenatal assessment of CHI is important for decreasing severe perinatal complications. Marchaudon *et al.* noted increased ALP in more than half of the CHI cases, and that it was associated with the severity of FGR or the extent of fibrin deposition.⁸ They also put forward the very interesting suggestion that the ALP released into the maternal circulation reflects the syncytiotrophoblastic lesions caused by histiocytosis in the intervillous space, and that the fibrin deposition covering the damaged villous cells could lead to placental insufficiency,⁸ although damage to villous cells in CHI has not been verified. In the present case, an extremely heightened ALP level was observed in the sixth and seventh pregnancies, but, despite this, each pregnancy had different clinical and pathological results, suggesting that although elevated ALP may indicate CHI, it does not necessarily reflect the severity of the clinicopathological status.

To manage CHI, obstetricians and pathologists must be aware of this unique pathological condition and accumulate data on the clinical course of complicated cases. More prospective multicenter studies are needed to develop an effective method of monitoring the extent of CHI and preventing progression. Also, more basic studies are required to clarify the pathophysiological mechanisms peculiar to CHI such as the unusual mobilization of maternal immune cells, non-destructive influence on villous tissue, and intervillous fibrin deposition. Such basic

research on CHI could also contribute to elucidation of the operation of the maternal immune system during pregnancy.

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Disclosure

The authors declare no conflict of interest.

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