

Case Series

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A Series of Rare Chronic Histiocytic Intervillitis Cases and its Association With Fetal Growth Restriction

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ABSTRACT

Objective: To re-evaluate a series of 6 diagnosed cases of chronic histiocytic intervillitis (CHI) its relation to recurrent pregnancy losses, and fetal growth restriction (FGR).

Methods: A retrospective study was conducted where patients were identified from the Department of Obstetrics and Gynecology database in Sant Joan de Deu Hospital (HSJD), Barcelona, Spain, between 2012 and 2016.

Results: Six cases were identified. All the 6 cases (100%) had a significant history for early pregnancy losses. Two patients had a previous history of recurrent pregnancy losses (>3) prior to spontaneous preterm labor of growth restricted fetuses with pathological utero-placenta doppler studies (33.3% of cases). The common factor among all patients was the smoking habits for more than 5 cigarettes per day and early pregnancy losses in the first trimester. In addition, maternal blood analysis showed increased neutrophils percentages and absolute values in 80% of the cases. Placental histological examination was significant for diffuse infiltration of the intervillous space prominently with cluster of differentiation 68 (CD68) positive macrophages and variable amounts of fibrinoid material deposition.

Conclusion: The mononuclear nature of the inflammatory cell infiltrate and the fibrin deposition in the placenta suggests an immunological insult. Hence, we hypothesize that the maternal immune system plays a key role in these cases. Also, our report data is consistent with the known association of chronic histiocytic intervillitis and recurrent pregnancy losses and FGR. In addition, these results support the notion of the negative impact of maternal smoking on pregnancy and fetal growth. Herein, we recommend conducting further studies to unravel the unknown pathophysiology of this disease in order to improve pregnancy outcomes.

KEYWORDS: Chronic histiocytic intervillitis; Fetal growth restriction; Recurrent pregnancy loss.

INTRODUCTION

In 1987, chronic histiocytic intervillitis (CHI) of the placenta has been described for the first time as a rare placental lesion (less than 1% of pregnancies).¹ Yet, the exact etiology of histiocytic intervillitis is still unknown. CHI is characterized with extensive infiltration of inflammatory mononuclear cells (monocytes, lymphocytes, histiocytes), from maternal origin, predominantly in the intervillous space of the placenta with the accumulation of non-circulating histiocytic cells. Currently, extensive body of evidence is correlating CHI to placental insufficiency related adverse pregnancy outcomes including high recurrent rate of pregnancy loss in subsequent pregnancies and FGR.²

To understand this rare condition, a retrospective case-cohort study was conducted intended to (a) identify the relevant obstetric characteristics of pregnancies complicated with CHI

and (b) to establish a correlation between the pathologic characteristics of intervillitis and the adverse pregnancy outcomes.

MATERIALS AND METHODS

Study Design

Cases of CHI from 2012 through 2016 were selected from the patients' records of the Department of Obstetrics and Gynecology with cross reference with the Department of Pathological Anatomy at HSJD, University of Barcelona, Barcelona, Spain. The Hospital's Institutional Review Board (IRB) approved the protocol. All the women signed an informed written consent. The methods were implemented according to approved guidelines. For each patient obstetrical data, parity, outcome of pregnancy and the mode of delivery were collected. Also, placental histology and immunohistochemistry data were retrieved from the Department of Pathological Anatomy.

Inclusion criteria

- All pregnant women admitted to HSJD from 2012 to 2016 for miscarriage and/or delivery where the pathology report can be retrieved.

Exclusion criteria

- Cases diagnosed with congenital malformations.
- Cases where deliveries have taken place in other hospitals.
- Cases with no pathological report.

Routinely, all products of conception and/or placental samples of adverse pregnancy outcomes are evaluated in the Department of the Pathological Anatomy as part of the standard clinical care. All placentas were fixed in paraffin/formaldehyde after basic gross examination. Placental blocks of the selected cases were retrieved. Serial sections (5 µm) of tissues embedded in paraffin blocks were prepared and stained with hematoxylin-eosin (Figures 1 and 2). Placental tissues were evaluated with a panel of antibodies CD68 (mononuclear phagocytic lineage), CD3 (T cells) and CD8 (cytotoxic cells). Immunostaining was performed using the standard immunohistochemical protocol. All the slides were examined by the same pathologist.

RESULTS

In this cohort of patients placentas examined at the Department of Pathological Anatomy, six cases of CHI were detected. Clinical characteristics of the 6 patients diagnosed with CHI are

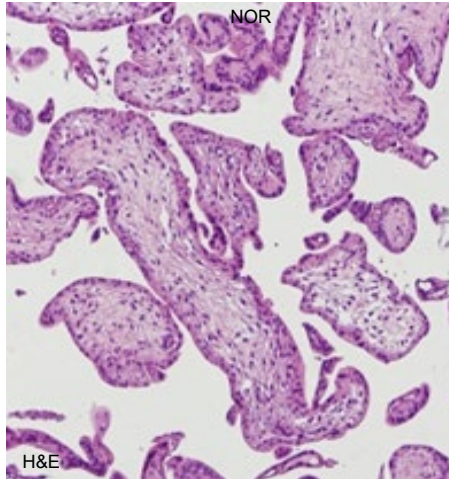


Figure 1: Normal Placenta (H&E, 200x).

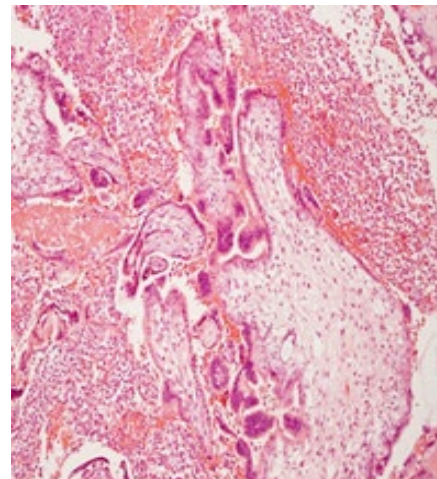


Figure 2: Histiocytic infiltrate in the intervillous space of paraffin-embedded placental section stained with H&E x100.

Patient	Age	Race	Parity	Gestational Age	Pregnancy outcome	Fetal weight
1	32	Spain	G6P1	8.6 Weeks	Abortion	-----
2	33	Spain	G3P1	33 Weeks	Severe FGR Previous history of Abortion	1290
3	36	Spain	G3P1	11 Weeks	Abortion	-----
4	36	Latin	G5P1	8 Weeks	Previous history of FGR Previous history of Abortion	2100
5	33	Spain	G2P0	12 Weeks	Abortion	-----
6	39	Spain	G2P0	8 Weeks	Blighted Ovum	-----

G: Gravidity, P: Parity, FGR: Fetal growth restriction.

Table 1: Perinatal data.

shown in Table 1.

The mean age of the patients is 34 years. Racial composition is mostly of European decent, however, one patient is Latino (16.7%). Medical history was unremarkable except for recurrent pregnancy losses in the 1st trimester in 5 cases (83.3%). Four of the patients had a history of recurrent pregnancy loss and prenatal smoking >5 cigarettes per day (66.7% of patients). None of the cases had a history of travelling to malaria endemic areas. Two cases of the 6 (33.3%) had both recurrent pregnancy losses (>3 recurrent successive losses) and preterm delivery of growth restricted fetuses with pathological uterine doppler.

Maternal peripheral blood differential count analysis, of the 1st trimester, showed increased neutrophils percentages and absolute values in 5 cases (83.3%), decreased eosinophils and lymphocytes percentages in all cases (100%). Severe FGR complicated 2 pregnancies, and recurrence of CHI in subsequent pregnancies was documented in 5 cases (83.3%). All of the described 1st trimester cases with CHI had normal karyotype.

To summarize some of the most important findings: 66.3% of patients carried a diagnosis of recurrent spontaneous abortion (3 or more consecutive losses), 33.3% of all gestations reaching the 2nd or 3rd trimester had FGR.

All of the tested cases showed uniform immunohistochemical staining for CD68. The latter is an antigen uniformly expressed in cells of the mononuclear phagocyte lineage which confirmed the histiocytic origin of the infiltrate (Figure 3). Also, all placental pathology exams showed mononuclear cellular infiltrate, predominantly histiocytic, in the intervillous space

(Figure 2) and intervillous fibrinoid deposition with intermediate trophoblast (Figure 4), a common finding in first trimester examined placentas. All cases have been examined to exclude any placental infections including viral or malarial.

DISCUSSION

CHI is a rare disease of unknown etiology. Placental lesions are characterized with mononuclear cells intervillous infiltrate and intervillous extensive fibrinoid deposit (Figures 2 and 3). A few T-cells and eosinophils may be present; and trophoblastic necrosis is a variable features.

In the literature, other minor forms have been described as the histiocytes accumulate in few areas of the placenta, called focal CHI.⁴ Various inflammatory patterns of chronic villitis have been documented including lymphohistiocytic, lymphocytic, lymphoplasmocytic lesions, and granulomatous inflammation with multinucleate giant cells.⁵ Meanwhile, CHI and villitis of unknown etiology (VUE) may coexist as they share some similarities such as histiocytic predominance.⁶ However, the intervillous infiltrate in VUE is polymorphic, consisting mainly of mononuclear cells of varying morphology, lymphocytes, giant cells, necrosis, fibrosis, granulation tissue and occasional neutrophils in the villous stroma. Mostly, these cells congregate near the villi rather than in the intervillous space.⁷ It is considered a common finding in normal and complicated pregnancies, hence it is believed that VUE may have an immunological origin.

CHI has been diagnosed in some cases with malarial infection. However, placental malaria is differentiated by the presence of histiocytes containing pigmented depositions of hemo-

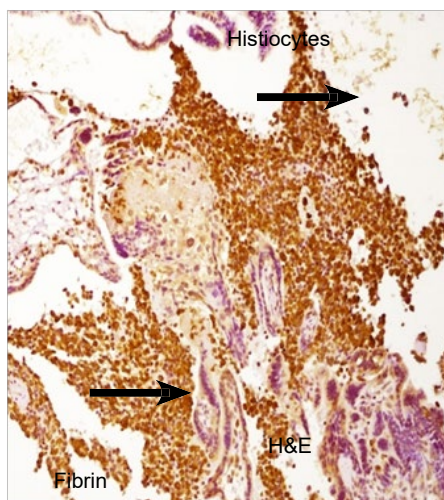


Figure 3: Histology & immunohistochemistry of CHI shows diffuse infiltration of the intervillous space by histiocytic cells. Majority of inflammatory cells stain for CD68, a monocyte-macrophage marker (CD68, 100x).

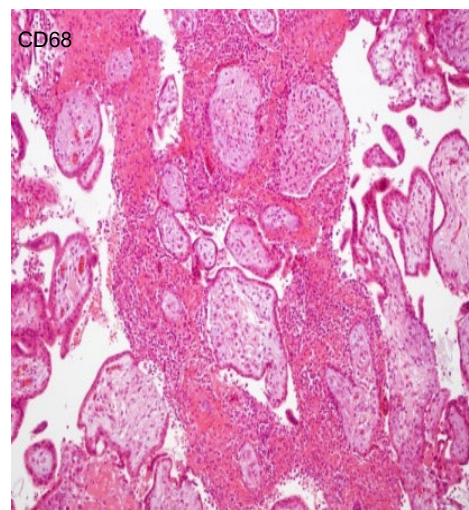


Figure 4: Massive chronic intervillitis. Maternal histiocytes fill much of the intervillous space admixed with an increased amount of fibrin shown by black arrow (H&E, 200x). All images are produced with DP20 Camera (Olympus, Hamburg, Germany).

zoa or parasitized erythrocytes and there is usually also evidence of villous damage.⁸ Furthermore, neutrophils and areas of villous syncytial necrosis are generally observed, and fibrin deposits in malaria lack the fibrinoid character and intermediate trophoblast seen with CHI. In all our 6 cases, none of our patients had a travel history to malaria-endemic areas and the malaria infection was excluded after placental examination. Viral placental infections should be included in the differential diagnoses as well. However, they display significant intervillitis and exhibit diffuse villitis and villous scarring. Intervillitis in these infections is mainly neutrophilic predominance and associated with acute villitis or intervillous abscess formation. These findings were not noted in our placental exams. One last idiopathic placental lesion is the maternal floor infarction, which is easily diagnosed by the deposition of fibrin in the decidua beneath the placenta rather than arterial occlusion and ischemic necrosis of the villi and not including any inflammatory component.^{9,10}

CHI has no specific clinical symptoms and signs suggesting its diagnosis. However, CHI has a high tendency for recurrence and increased rates of unfavorable perinatal outcomes including recurrent spontaneous abortions, perinatal mortality and FGR. The only biomarker which can be used to detect CHI is alkaline phosphatase (ALP); yet the latter is not specific to establish a diagnosis. CHI is exclusively diagnosed postnatal by histopathological evaluation of the placenta. In the meantime, routine histologic evaluation of the first trimester spontaneous abortions is rarely performed however, one study of about 700 1st trimester miscarriages detected that 4.4% of the examined placentas were diagnosed with CHI.⁷

Meanwhile, studies have shown that CHI diagnosed cases may result in approximately 70% live births with placental insufficiency and FGR as the most common complications.¹¹ FGR is defined as fetal weight less than 10% in correspondence to the gestational age. In cases of FGR, uterine doppler flow studies are used to assess the placental vasculature and resistance. Hence, abnormal uterine doppler studies reflect placental insufficiency and the increased placental resistance from the maternal side.¹² Two of our cases showed pathological doppler studies associated with FGR. These findings are in line with the CHI placental malfunction. In a study of 211 placentas, the incidence of CHI was increased among the low birth weight infants of all the studied cases.¹³ In another study, it was noted that villitis was the most frequent pathologic placental finding in normotensive-term pregnancies with FGR.¹⁴ Therefore, it has been recommended that chorionic villus sampling may be performed to evaluate both CHI and karyotyping in all pregnancies with severe FGR.

It has been postulated that an immuno-inflammatory trigger is a possible pathomechanism of CHI due to (a) the presence of maternally derived mononuclear cells, (b) increased presence of inflammatory cells, and (c) the presence of acute atherosclerosis-like lesions in the decidual vessels with Immunoglobulin M (IgM) and complement deposits.¹⁵ Another piece of evidence that supports the above mentioned notion is that CHI has

been reported to be associated with antiphospholipid antibodies and systemic lupus erythematosus. These morbidities have been known to trigger the maternal immune system.¹⁶ Others have considered pregnancy as an allograft bearing foreign, paternally derived antigens transplanted into the maternal uterus.⁷ Hence, suppression or modulation of the maternal immune reactivity to these foreign antigens is mandated to protect the fetus. One of the fetal protection postulated mechanisms is deviation of the maternal local inflammatory cells away from a delayed hypersensitivity-type response (known as TH1) towards a TH2-type response.¹⁷ Simultaneously, the placenta is infiltrated by maternal immune cells: macrophages, T-lymphocytes, and natural killer (NK) cells early in pregnancy to support maternal tolerance to paternal antigens.¹⁸ As a result, maternal activated macrophages, lymphocytes (CD3+) cells, and specific cytokines, such as gamma-interferon and tumor necrosis factor- α (TNF- α), are strictly regulated within the placentas. That may explain the presence of mononuclear cells in the placentas of CHI.

It is well known that during gestation neutrophil counts gradually increase starting from the 1st trimester and the lymphocyte count tends to decrease by the end of gestation.¹⁹ Our data showed increased neutrophils count (percentages and absolute values) in 5 cases (83.3%), decreased eosinophils and lymphocytes percentages in all cases (100%) in the first trimester maternal peripheral blood testing in comparison to normal gestational aged matched pregnancy. Given our limited number of cases, however it may suggest an exaggerated maternal immune-inflammatory response associated with CHI cases.

Furthermore, it is believed that the inflammatory process in CHI leads to luminal obliteration and/or thrombosis, resulting in avascular villi. However, the stronger impact of immunological changes is suggested to play the major role. Of note, CHI has been shown to be associated with assisted reproductive techniques in very small percentages of cases.²⁰ What triggers these immunologic events is obscure, but the presence of villitis in normal placentas supports the above mentioned notion.

Owing to the high recurrence rate of the lesion, and CHI does not present with any specific symptoms during gestation, it is recommended that these patients should be treated as being at high risk in their subsequent pregnancies. Though, there is no established therapeutic protocol and the assumption of immune mechanism is involved in the pathogenesis of placental lesions has led to the proposal of immunosuppressive and thrombolytic therapy. Also, treatment with corticosteroids and aspirin has been attempted in few cases.²¹ However, due to the rarity of the disease, there is not sufficient data to support such treatment. Hence, more studies are required in order to understand the mechanism of CHI and its management.

We acknowledge the limitations in this review as the number of diagnosed cases is limited, due to the rarity of the condition. However, in this report, we present new evidence for the association between CHI and adverse pregnancy outcomes particularly, FGR. Furthermore, to our knowledge, this is the

first article showing clinical signs during gestation in cases of CHI: the abnormal Doppler studies. Also, we have shown differences in the maternal peripheral blood immune cells in cases of CHI in comparison to the controls in the first trimester. This may suggest either that the maternal immune system has been prematurely triggered resulting in placental pathology or cases of CHI has an early influence on the maternal immune cells.

CONCLUSION

CHI is a rare disease of unknown etiology. It is only diagnosed postnatal. Yet, CHI has a big impact on the female reproductive capacity. The condition has a high recurrence risk in subsequent pregnancies, associated with pregnancy losses, and FGR. Hence, it is essential to recognize CHI and report it once diagnosed. Moreover, it is essential to differentiate CHI from chronic villitis and other forms of placental lesions.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

CONSENT

The authors obtained written informed consent from the patient for submission of this manuscript for publication.

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