Chronic Histiocytic Intervillositis: A Placental Lesion Associated With Recurrent Reproductive Loss

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Chronic (histiocytic) intervillositis (CHIV), defined for the purposes of this study as diffuse histiocytic infiltration of the intervillous space without villitis, is an idiopathic lesion seen in the chorionic sacs of some spontaneous abortion specimens and placentas. In this retrospective study, we evaluated all patients diagnosed with CHIV from 2 hospitals between 1993 and 2000, plus 1 additional patient from 1977. Histopathology, phenotype of the leukocytic infiltrate, perinatal outcome, and other associated clinical features were assessed by review of clinical records and all available pathology specimens plus immunohistochemical staining. CHIV was found in 31 of 45 specimens examined from 21 patients (23 of 31 first trimester, 3 of 5 second trimester, and 5 of 9 third trimester). Recurrence rate was 67% for patients with more than one specimen reviewed. Overall perinatal mortality rate was 77%, and only 18% of pregnancies reached 37 weeks. Eight of 19 patients with 3 or more pregnancies had recurrent spontaneous abortion (RSA); 5 with primary RSA (≥3 consecutive spontaneous abortions (SAB) with no living children) and 3 with secondary RSA (≥3 consecutive SAB with 1 or more living children). Severe intrauterine growth restriction was seen in 5 of 8 second- and third-trimester placentas with CHIV. Patients were generally not of advanced maternal age (mean, 29.8 ± 6.2 years), and there was no obvious racial predisposition. Autoimmune or allergic phenomena were identified in 11 patients. Immunohistochemical staining of the intervillous infiltrate showed a near uniform population of monocyte-macrophages at varying stages of maturity and activation: more than 90% CD45Rb and CD68 positive, 30% to 40% MAC387 positive, less than 5% CD3 positive, and CD1a, CD20, CD30, and CD56 negative. We conclude that CHIV is an uncommon but important cause of recurrent spontaneous abortion and, in some cases, loss at later gestational ages. HUM PATHOL 31:1389-1396.

Key words: **intervillous space, idiopathic chronic inflammation, macrophage, massive chronic intervillositis, placenta, spontaneous abortion, reproductive immunology.**

Abbreviations: **CHIV, chronic histiocytic intervillositis; IUGR, intrauterine growth restriction; RSA, recurrent spontaneous abortion; TH1, T-helper lymphocyte-type 1; TH2, T-helper lymphocyte-type 2; NK, natural killer.**

Recurrent pregnancy loss is a poorly understood problem of major concern for a subgroup of couples attempting to start a family.[1,2] Individual patients may present with isolated infertility, recurrent spontaneous abortion, or repeated second- and third-trimester loss. However, epidemiologic evidence suggests strong interrelationships between these adverse outcomes.[3] Recognized causes of recurrent pregnancy loss include hormonal imbalance, reproductive tract anomalies, genetic or chromosomal abnormalities, psychosocial factors, autoimmune diseases, and possibly maternal-fetal immunologic incompatibility. Most cases are inadequately explained.

The pathology of recurrent pregnancy loss is even less understood, with only 3 well characterized syndromes in the literature: maternal floor infarction, chronic villitis, and thrombophilia-associated maternal vasculopathy.[4-6] In this report, we describe clinical and pathologic aspects of a fourth cause of recurrent fetal loss, chronic histiocytic intervillositis—also known as "massive chronic intervillositis"—in a retrospective study of 31 cases from 21 patients diagnosed at 2 large high-risk obstetric and perinatal centers.

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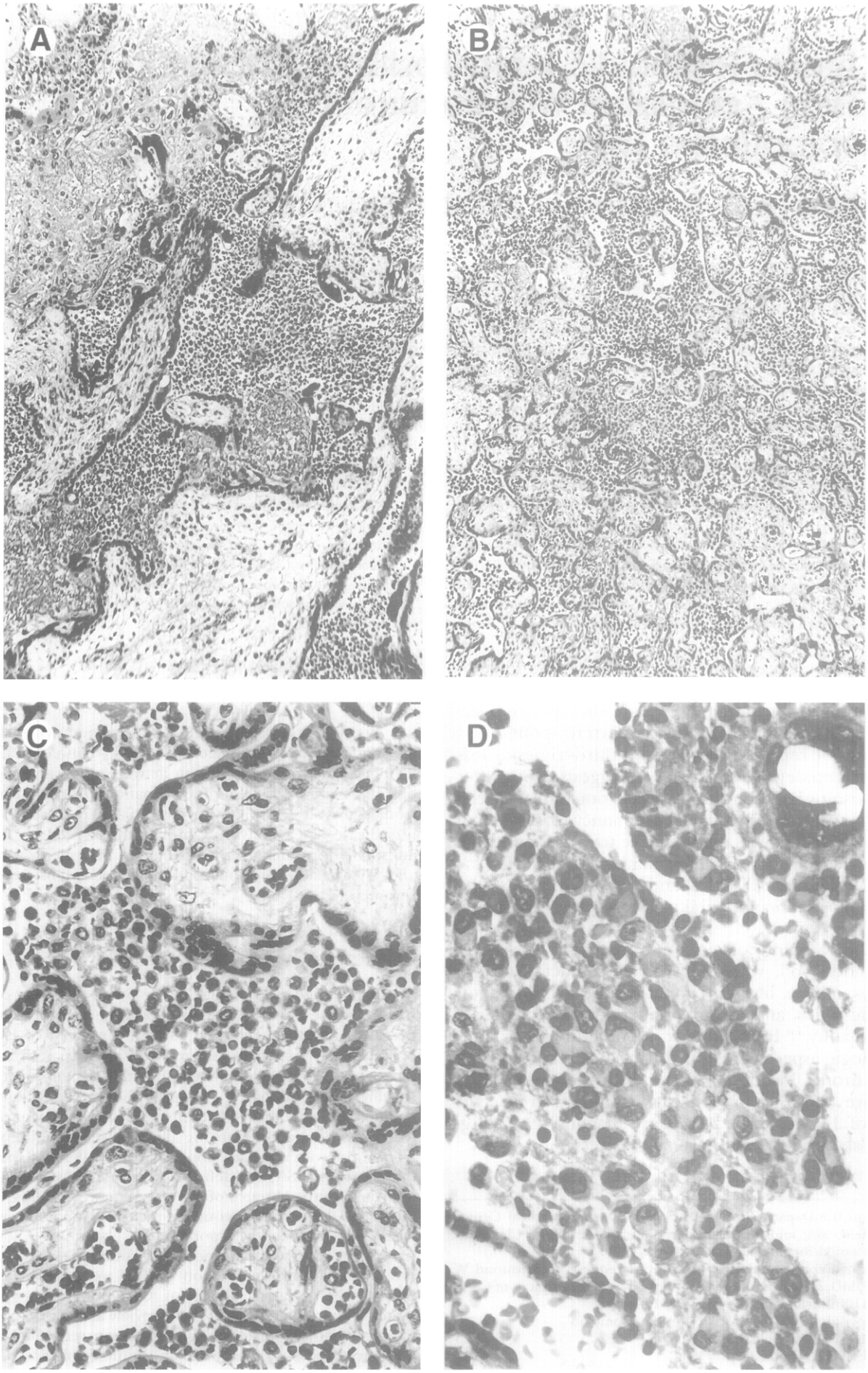
MATERIALS AND METHODS

Study Design

This was a retrospective study of all patients ($n = 20$) with chronic histiocytic intervillositis (CHIV) between 1993 and 2000 at 2 medical centers with active routine and high-risk obstetric services. One additional patient diagnosed in 1977 from University Hospitals was also included (case 21). Each index case of CHIV was examined and agreed on by both authors before inclusion in the series. Past medical records and all available previous pathology specimens were then reviewed.

Clinical History

Patient age refers to age at the time of delivery or evacuation of the index specimen. Nonwhite race, for the purposes of this study, refers to African American or Hispanic origin as designated in the medical records. Autoimmune disease was broadly defined and included patients with organ-specific autoantibodies, antiphospholipid antibody syndrome, and sarcoidosis. Patients recorded as having asthma with or without accompanying allergies were listed separately from those with allergies alone. Primary recurrent spontaneous abortion (RSA) was defined as 3 consecutive spontaneous abortions in the absence of any pregnancy extending beyond 20 weeks' gestation. Secondary recurrent abortion was defined as 3 consecutive spontaneous abortions following a pregnancy of 20 weeks or more. Infertility, preeclampsia, and intrauterine growth restriction (IUGR) were diagnoses made by the original caring physicians. Gestational ages were estimated by a combination of chart review and pathologic staging as previously described.[7] Information regarding gender and karyotype was obtained from the medical records.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Pathology

A representative slide from each specimen with CHIV was graded on a 1 to 3 qualitative scale for the number of histiocytes and the amount of fibrinoid material in the intervillous space. Averages and standard deviations of the 2 scores were calculated. CD68 stains were performed in a total of 10 of 31 cases to assist in making the diagnosis. Six cases (2 each from the first, second, and third trimester) were selected and studied by immunocytochemistry with a battery of lineage-specific antibodies by using previously published standard methods for paraffin-embedded tissues.[8] Antibodies (Dako, Carpenteria CA) specific for the following antigens were used (lineage specificity in parentheses): CD1a (immature dendritic cells[9,10]), CD3 (T cells), CD20 (B cells), CD30 (TH2 T cell subset[11,12]), CD45Rb (pan leukocyte), CD56 (natural killer [NK] cells), CD68 (mononuclear phagocyte lineage[13]), and MRP14 (activated immature monocyte-macrophage subset[14-16]).

RESULTS

CHIV, for the purposes of this study, was defined as monomorphic infiltration of the placental intervillous space by cells identifiable as belonging to the mononuclear phagocyte lineage (histiocytes) by morphologic criteria (Fig 1). Cases with polymorphic intervillous infiltrates (ie, histiocytes plus lymphocytes, neutrophils, or eosinophils) by light microscopy or with any evidence of chronic villitis (inflammation of the villous stroma) were specifically excluded. All cases tested (10 of 10) showed uniform immunohistochemical staining for CD68, an antigen uniformly expressed in cells of the mononuclear phagocyte lineage. Six cases of CHIV, 2 from each trimester of pregnancy, were stained with a panel of antibodies to further characterize the intervillous infiltrate (Figs 2A, B). In addition to near uniform positivity (>90%) for CD68 and leukocyte common antigen (CD45Rb), a substantial minority of cells in the intervillous space (approximately 30% to 40%) also stained for the calcium-binding protein MRP14 (MAC387), an antigen expressed by activated immature monocyte-macrophages.[14-16] T lymphocytes (CD3 positive) were rare (<5% of infiltrating cells), and the following cell types were not detected: CD-1a–positive dendritic cells, CD20-positive B lymphocytes, CD30-positive TH2 cells, and CD56-positive NK cells. Sections of the decidua from 2 first-trimester cases were stained with antibodies to CD68 and CD56 (Fig 2C and D). CD68-positive cells were largely limited to decidual blood vessels in communication with the intervillous space. CD56-positive cells were equally frequent in the decidua of cases and normal control first-trimester abortion specimens (results for the latter not shown).

A total of 31 cases of CHIV were identified among 45 specimens reviewed from the 21 patients in this series (Table 1). Positive cases were separated by clinical gestational age and pathologic staging into 3 subgroups: <12 weeks (first trimester), 12 to 23 weeks (second trimester), and >23 weeks (third trimester). Most cases (74%) occurred in the first trimester, but the percentage of positive specimens in each trimester was similar (56% to 74%). In some specimens, histiocytes were accompanied by intervillous fibrinoid deposits containing intermediate trophoblast (Fig 1A). Semiquantitative grading by the 2 authors indicated that the number of histiocytes increased and the amount of intervillous fibrinoid decreased with gestational age. Information regarding gender was not uniformly available, but a female predominance (68% overall) was noted among affected specimens in all 3 trimesters that was not seen in the unreviewed specimens (50% female). Karyotypes were infrequently performed (13 cases). Three abnormal karyotypes were detected: 45,X, 96,XXXX, and 46,XX,del(1)[2]/46,XX[10], each occurring in a different patient. Prevalence of IUGR in second and third trimester cases was high (5 of 8 cases).

Clinical characteristics of the 21 patients with CHIV are shown in Table 2. The mean age of the mothers at the time of accession of the index specimen was 29.8 ± 6.2 years. Racial composition, as designated in the clinical chart, showed a predominance (52%) of nonwhite patients which roughly mirrored the populations served by the 2 hospitals. Medical history was unremarkable, with the exception of autoimmune and allergic conditions, identified in 52% of patients (3 with autoimmune disease, 5 with asthma, and 3 with drug allergies). Eight patients had recurrent spontaneous abortion (3 or more consecutive spontaneous abortions); 5 with primary RSA (no living children) and 3 with secondary RSA (1 or more living children). History of infertility and preeclampsia without other reproductive disorders was present in 1 patient each.

Overall pregnancy outcome for patients with 1 or more cases of CHIV is presented in Table 3. Of note are the high overall rates of perinatal mortality (77%, only 22 living children) and spontaneous abortion (52%) and the low number of pregnancies reaching term (18%). In addition to the 8 patients with RSA, 5 of the remaining 10 patients with more than 1 pregnancy had 2 or more spontaneous abortions. The rate of docu-

FIGURE 1. Typical light microscopic features of CHIV. (A) First-trimester spontaneous abortion from a patient with recurrent spontaneous abortion (Case 10), showing massive infiltration of the intervillous space by a uniform population of mononuclear cells of histiocytic morphology. (H&E, original magnification ×200.) Intervillous fibrinoid deposition with intermediate trophoblast, a common finding in first trimester CHIV, is seen at the upper left. (B) 39-Week placenta from a patient with preeclampsia (case 11) with intervillous infiltrate similar to that seen in A, but without prominent intervillous fibrinoid. (H&E, original magnification ×200.) (C) Higher-power micrograph of case 11, showing histiocytes at varying stages of maturation. (H&E, original magnification ×500.) (D) High-power magnification of cells from case 10, showing detailed cytologic features of histiocytes. Two major forms are seen: one with bean-shaped hyperechromatic nuclei and scant cytoplasm and the other with eccentric, less hyperchromatic nuclei of similar conformation and prominent eosinophilic cytoplasm with perinuclear clearing. Occasional binucleate cells are present. (H&E, original magnification ×800.)

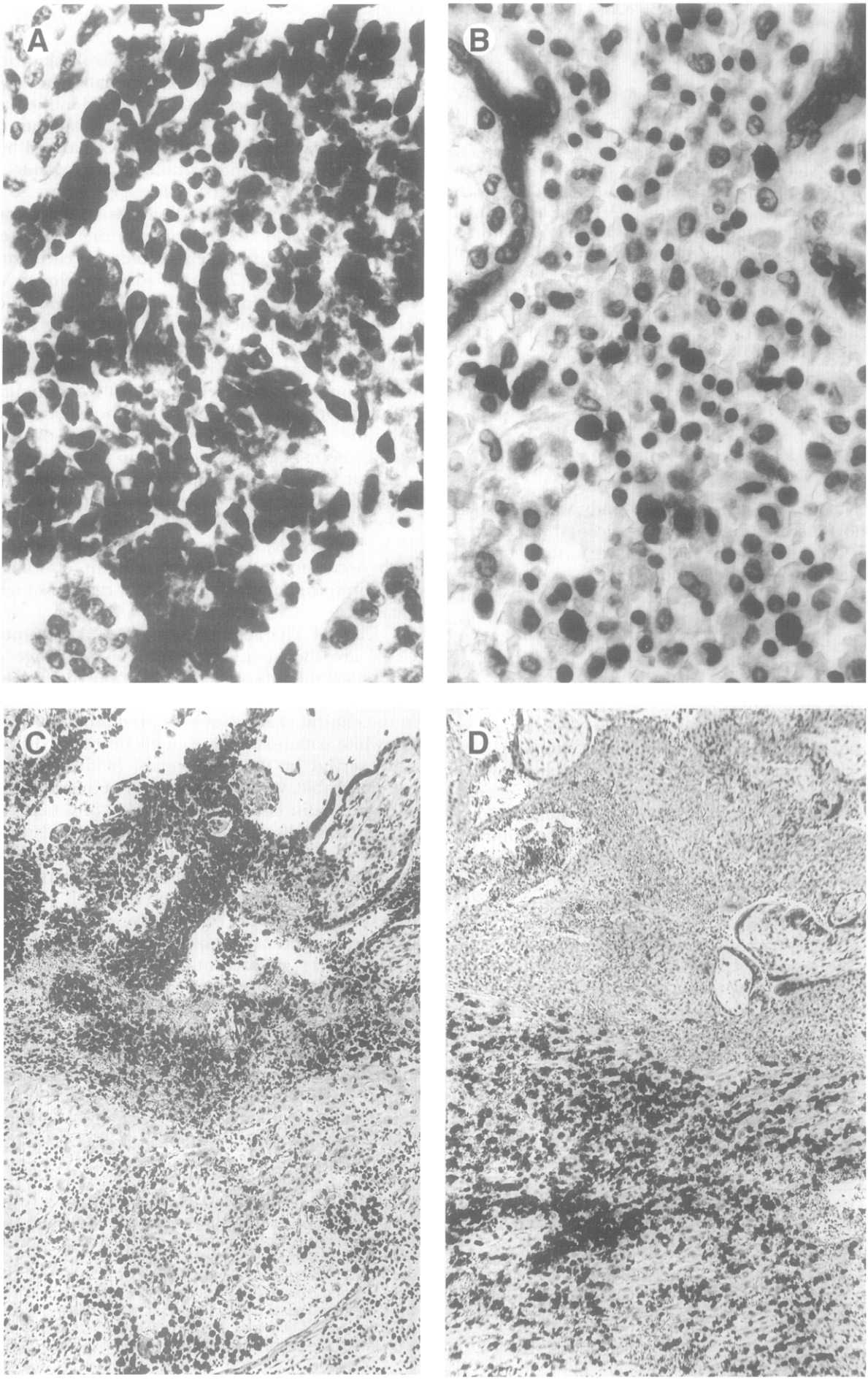
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Table 1. Summary of CHIV Cases

	1st Trimester	2nd Trimester	3rd Trimester	Total
No. of pregnancies	52	7	23	82
No. examined	31	5	9	45
CHIV-positive	23	3	5	31
Male sex	4/11	1/3	1/4	6/19
Abnormal karyotype	3/11	0/2	NA	3/13
IUGR	NA	1/3	4/5	5/8
Grade*/histiocytes	1.9 ± 0.7	2.0 ± 0.6	2.4 ± 0.5	—
Grade/fibrinoid	2.3 ± 0.5	2.2 ± 0.8	1.0 ± 0.0	—

*One slide from each specimen semiquantitatively graded from 0 to 3 by 2 observers. Value is mean ± standard deviation of the average score for each slide.

mented recurrence for CHIV in our series was 67% (6 of 9 patients with 2 or more specimens reviewed).

DISCUSSION

We found 55 previously reported cases of chronic intervillositis in the literature. Twelve were published as abstracts only. Nineteen (including 8 of the cases in this report) were included with little detail in 2 large series of first-trimester abortions.[7,17-22] Five of the remaining 28 cases had coexistent chronic villitis and therefore did not qualify as CHIV according to the definition used in this report. Data from these previous reports corroborate a number of our findings. CHIV has been described in both spontaneous abortions and third-trimester placentas. Autoimmune phenomena were reported in 3 patients. Severe IUGR complicated 5 pregnancies, and recurrence of chronic intervillositis in subsequent pregnancies was documented in 2 cases. Most of the previously described first-trimester cases with chronic intervillositis had a normal karyotype.

The current report describing 31 cases of CHIV in 21 patients extends the clinical profile and provides a more complete description of the pathologic features at various gestational ages. Overall prevalence of CHIV among specimens submitted to pathology at one of the institutions (UH) was 9.6 per 1,000 spontaneous abortions and 0.6 per 1,000 second and third trimester placentas. Previous data from our institution have shown that the prevalence of CHIV is increased among spontaneous abortions with a normal karyotype (22 of 1,000) and markedly increased in patients with a history of prior spontaneous abortion (80 of 1,000).[7] There was no racial predominance in the current study. Patients were generally not of advanced maternal age. Overall mean age at diagnosis of CHIV was 29.8 years in the current study, as compared with 29.9 years in our previous study of all spontaneous abortions. Patients with RSA and CHIV in the current study were younger than patients from our previous study having RSA of any cause (27.8 *v* 35.0 years). Autoimmune and allergic diseases were common in patients with CHIV, but these findings are difficult to interpret without background information regarding their prevalence in our population. The most striking characteristic of patients having at least 1 specimen with CHIV was poor obstetric history. To summarize some of the most important findings: 59% of pregnancies ended in spontaneous abortion, 38% of patients carried a diagnosis of recurrent spontaneous abortion by stringent criteria (3 or more consecutive losses), 27% of all gestations reaching the second or third trimester had IUGR, and 67% of patients with more than 1 specimen available for review had recurrence of CHIV in subsequent pregnancies.

The differential diagnosis of CHIV includes 4 entities. The most important condition to be excluded is the chronic stage of placental malaria.[23-25] Intervillous histiocytes are typical of both conditions. However, the intervillous space in malaria also invariably contains either hemozoin pigment or parasitized red blood cells. 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 CHIV. None of our patients had a history of travel to malaria-endemic areas. The second consideration would be other unusual infections. Viral infections of the placenta rarely show significant intervillositis and almost always have diffuse villitis and villous scarring. Other organisms known to be associated with intervillositis include *Listeria monocytogenes, Campylobacter fetus, Francisella tularensis,* and *Coccidioides immitis.*[26-29] However, the intervillositis in these infections is predominantly neutrophilic and often accompanied by acute villitis or intervillous absess formation. Although not obtained in every instance, special stains for fungi and bacteria were uniformly negative in our cases. Absence of any clinical signs of infection, negative travel history, and recurrence of CHIV in subsequent pregnancies are additional factors arguing against the infections listed above. The third entity, villitis of unknown cause with coexisting intervillositis, was excluded by definition from our cases. Furthermore, the intervillous infiltrate in villitis of unknown cause is polymorphic, consisting of mononuclear cells of varying morphology,

FIGURE 2. Immunocytochemical staining pattern of CHIV (peroxidase-diamniobenzidine with hematoxylin counterstaining). (A) CD68 stain showing uniform staining of virtually all cells in the intervillous space, indicating that they belong to the mononuclear phagocyte lineage. (Original magnification ×800.) (B) MAC387 (MRP14) stain showing intense staining of approximately 30% of cells (small round to ovoid cells with uniform dense black staining), primarily those of the smaller subset described above, indicating that they are activated immature monocyte-macrophages. (Original magnification, ×800.) (C) CD68 staining of the junctional region between intervillous space and implantation site, showing uniform positivity for cells in the intervillous space. CD68-positive cells in the decidua are primarily confined to the large vessel at the bottom center of the figure, which communicates with the intervillous space. (Original magnification × 200.) (D) CD56 staining of the same regions shown in C, showing diffuse infiltration of the decidua by CD56-positive cells of the NK lineage without any spillover into the intervillous space. The number of CD56 cells is indistinguishable from normal control pregnancies. (Original magnification ×200.)

Table 2. Demographic Characteristics and Clinical History of Patients With CHIV

Case No.*	Age†	Nonwhite	Autoimmune	Asthma	Allergy	Primary RSA‡	Secondary RSA§
1	32	1	1	0	0	1	NA‖
2	33	0	0	1	0	0	NA
3	33	0	0	0	1	0	1
4	28	0	0	0	0	1	NA
5	31	0	0	0	0	0	0
6	34	0	0	0	0	0	NA
7	27	0	0	1	0	1	NA
8	25	1	0	1	0	0	1
9	20	1	0	0	0	NA	NA
10	31	1	0	0	0	1	NA
11	20	1	0	0	0	NA	NA
12	39	1	1	0	0	0	NA
13	22	1	0	0	0	NA	NA
14	39	0	0	0	1	0	0
15	28	1	0	1	1	0	1
16	22	1	1	0	0	NA	NA
17	27	0	0	0	1	NA	NA
18	43	1	0	0	0	NA	NA
19	30	0	0	0	0	0	NA
20	33	1	0	0	0	NA	NA
21	28	0	0	1	0	1	NA
	29.8 ± 6.2¶	11	3	5	3	5/14	3/5
		(52)**	(14)	(24)	(14)	(36)	(60)

*Case nos. 1 through 9 are from Baystate Medical Center; cases 10 through 21, from University Hospitals.
† Age at diagnosis of the index specimen.
‡ ≥ 3 consecutive SA without a living child.
§ ≥ 3 consecutive SA after a living child.
‖ NA = not applicable, insufficient number of pregnancies.
¶ Mean ± standard deviation.
** (Percent positive).

lymphocytes, and occasional neutrophils, and tends to congregate near villi (perivillitis) rather than in the intervillous space (intervillositis).[30] The final consideration is the idiopathic placental lesion known as "maternal floor infarction."[5,31] Several characteristics of CHIV including high recurrence rate, poor perinatal outcome, broad gestational age range, and association with autoimmune phenomena overlap with this lesion. In the current study, most cases of first trimester CHIV showed prominent intervillous fibrinoid with interme-

Table 3. Obstetric History of Patients With CHIV

Case No.*	Total Pregnancies	Term ≥37 weeks	Preterm 20-36 weeks	SA <20 weeks	Living Children	Elective Terminations	No. of Specimens CHIV
1	7	0	0	7	0	0	1
2	5	1	1	1	1	1	1
3	8	1	1	5	1	1	2
4	5	0	0	4	0	1	3
5	6	3	0	3	3	0	1
6	3	1	0	2	1	0	1
7	6	0	0	5	0	1	2
8	5	0	2	3	2	0	3
9	1	0	0	1	0	0	1
10	9	2	0	6	2	1	1
11	2	1	0	0	1	1	1
12	3	1	0	2	1	0	1
13	2	1	0	1	1	0	1
14	4	2	0	2	2	0	1
15	8	1	0	7	1	0	1
16	3	0	0	1	0	2	1
17	2	1	1	0	2	0	1
18	5	1	1	1	2	2	1
19	3	0	1	2	0	0	2
20	4	0	0	3	0	1	1
21	6	1	1	3	2	1	4
	97	17	8	50	22	12	31

* Case nos. 1 through 9 are from Baystate Medical Center; cases 10 through 21 from University Hospitals.

diate trophoblast, which is the sine qua non of maternal floor infarction. However, maternal floor infarction as currently defined does not include an inflammatory component, and it seems most reasonable to consider these 2 uncommon but important lesions as separate entities.

The underlying cause of CHIV is unknown. As discussed, the histologic pattern and clinical profile do not suggest infection. Pregnancy may be considered an allograft bearing foreign, paternally derived, transplantation antigens transplanted into the maternal uterus. Mechanisms that suppress or modulate reactivity to these foreign antigens are so pervasive that no clearcut example of fetoplacental rejection has yet been described in humans or in animal models. One of the many postulated mechanisms protecting the fetus is so-called immune deviation of local maternal inflammatory cells away from a delayed hypersensitivity–type response (also known as TH1) and toward an alternative pattern known as a TH2-type response.[32,33] As a consequence of TH2 deviation, certain maternal cells, such as activated macrophages and CD3-positive T cells, and specific cytokines, such as gamma-interferon and tumor necrosis factor-α, are strictly regulated within the placentas of animals and humans.[34-38] A well-established model of spontaneous abortion involving matings between 2 specific mouse strains (DBA/2 and CBA/J) is associated with a deleterious TH1-type response that can be reversed by manipulations promoting TH2 deviation.[39-41] A second murine model, leishmania infection during pregnancy, also leads to a TH1-type response and is associated with pregnancy loss.[42,43] In humans, a distinct subgroup of patients with recurrent spontaneous abortion have a TH1-type response to pregnancy, which includes a circulating embryotoxic factor subsequently shown to be gamma-interferon.[44,45] These patients can sometimes be effectively treated with treatment regimens believed to cause TH2 deviation.[46-48]

Although not definitive, features of CHIV favoring a TH1-type response include presence of morphologically activated macrophages and rare CD3-positive lymphocytes in the intervillous space and absence of cells commonly associated with TH2-type immune responses (CD30-positive T lymphocytes, CD1a-positive immature dendritic cells, and eosinophils).[11,49,50] A previously published patient with recurrent CHIV had a circulating embryotoxic factor that disappeared after immunomodulatory therapy (progesterone suppositories supplemented in 1 case with prednisone). Two successful pregnancies after treatment had a reduced degree of CHIV.[21] One of the patients in our series with CHIV and RSA (case 21) also had 2 successful pregnancies with decreased CHIV after treatment with progesterone. Finally, the histologic similarity between CHIV and placental malaria is intriguing. Malaria is associated with a dramatic increase in TH1 cytokines within the intervillous space.[38] These cytokines are known to activate macrophages and induce adhesion molecules on trophoblast, leading to the sequestration of macrophages and parasitized red blood cells in the intervillous space.[51-53] It is now widely believed that the high perinatal morbidity associated with malaria is attributable to the intervillous inflammatory process rather than maternal (or fetal) parasitemia.[25]

In conclusion, CHIV is an underrecognized placental lesion of unknown pathogenesis most common in first-trimester abortion specimens, but associated with recurrent reproductive loss at all gestational ages. Circumstantial evidence, including autoimmune and allergic conditions in the mothers, the phenotype of the intervillous infiltrate, and anecdotal reports of successful immunomodulatory therapy are suggestive of an immunologic causation, but infections or other nonimmune causes of inflammation cannot be excluded at this time.

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