Massive Chronic Intervillositis Associated With Recurrent Abortions

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Massive chronic intervillositis (MCI) is an unusual placental lesion associated with poor fetal growth and adverse pregnancy outcome; it has not previously been associated with spontaneous abortion or recurrent pregnancy loss. This article reports a patient who had 10 spontaneous abortions with repetitious massive chronic intervillositis documented in four of five gestations spanning all three trimesters. Characteristic placentopathy included massive infiltration of the maternal intervillous space by chronic inflammatory cells and fibrin, without associated chronic villitis; the cellular infiltrate was composed predominantly of LCA and CD68 immunoreactive cells with scattered CD45RO positivity, consistent with a monocyte/macrophage population with occasional T lymphocytes. Elevated maternal serum alpha-fetoprotein was documented in two pregnancies. These findings support the concept that this unusual placental lesion may have an immunologic basis, and suggest that MCI may be a histopathologically recognizable cause of recurrent spontaneous abortion. HUM PATHOL 26:1245-1251. Copyright © 1995 by W.B. Saunders Company

Key words: recurrent abortion, spontaneous abortion, intervillositis, chronic villitis, alpha-fetoprotein, TH1-type cytokines.

Abbreviations: MCI, massive chronic intervillositis; SAB, spontaneous abortion; LCA, leukocyte common antigen; HSV, herpes simplex virus; CMV, cytomegalovirus; PBMC, peripheral blood mononuclear cells; MSAFP, maternal serum alpha-fetoprotein; HAB, habitual abortion; CVUE, chronic villitis of unknown etiology; MFI, maternal floor infant; TH1, T helper 1.

RESULTS

Clinical History

A 36-year-old woman, gravida 13 para 2 abortus 11, had a history of 10 SABs. The first five SABs were consecutive and occurred between 11 and 18 weeks of gestation (Table 2; pregnancy nos. 2 to 6); histological material from two of these SABs was available for review (pregnancy nos. 3 and 6). Pregnancy no. 3, a SAB at 15 weeks, was associated with a maternal temperature of 101.3°F. During pregnancy no. 5, a SAB at 18 weeks, an elevated maternal serum alpha-fetoprotein (MSAFP) and an abnormal ultrasound (oligohydramnios with delayed fetal growth) were noted at 14 weeks, and intrauterine fetal death was diagnosed at 18 weeks. During pregnancy no. 6, a SAB at 11 weeks, an ultrasound at 6.5 weeks confirmed a gestational sac with a fetal pole and fetal heart beat.

Following pregnancy no. 6, medical evaluation for recurrent abortions showed a positive ANA (titer 1:40 to 1:320) with a speckled pattern. The anti-DNA titer was 1:80. Anticardiolipin, anti-Ro, and anti-La antibodies were not detected, and complement levels (C1q, C4, C3, C2) were within normal limits. CD 50 was 135 (normal range of 150 to 250). Thyroid function tests, Coombs’s antibody screen, rapid plasma reagin test, and cervical cultures for chlamydia and gonorrhea were all negative. A positive cervical mycoplasma culture was treated with tetracycline, and two subsequent cultures were negative. Lymphocyte cultures from the patient and her husband revealed normal karyotypes. The patient was also tested at the Harvard Recurrent Miscarriage Center with a new assay for embryotoxic T helper 1 (TH1)-type cytokines. The patient’s peripheral blood mononuclear cells

MATERIALS AND METHODS

Medical records, karyotypes, and placental histological slides were reviewed. From three to 11 slides per placenta were available from five pregnancies. Placental tissue was fixed in 10% buffered formalin, paraffin-embedded, sectioned, and stained with hematoxylin-eosin, Gram’s, and Steiner’s stains. Immunohistochemical studies were performed on paraffin-embedded tissue using antibodies recognizing CD45 (leukocyte common antigen [LCA]); CD45RO (UCHL1), a pan-T lymphocyte marker; L26, a pan-B lymphocyte marker; CD68 (KP1), a monocyte/macrophage marker; herpes simplex virus (HSV) I and II; and cytomegalovirus (CMV) (Table 1).

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(PBMCs) were cultured with a membrane protein extract derived from the trophoblast cell line JEG-3. The obtained culture supernatant contained a 10- to 30-KD heat-labile substance (embryotoxic factor) that inhibited the development of murine embryos in culture. The supernatant's embryotoxicity was removed after passage through a column containing anti-interferon-gamma-coated beads. In a subsequent PBMC culture, the addition of 10^{-5} M progesterone inhibited embryotoxic factor production.

Based on the foregoing assessment, pregnancy no. 7 was treated with progesterone vaginal suppositories (100 mg twice daily from 3 days after ovulation until 20 weeks of gestation). When reassessed at 6 weeks of gestation, embryotoxic factors were absent. The pregnancy progressed without difficulty and resulted in a 2,900-g (37th percentile) female infant delivered at 41 weeks of gestation.

The next five pregnancies (Table 2; pregnancy nos. 8 to 12) were recurrent SABs. Three SABs (pregnancy nos. 8, 10, and 11) were detected by hCG alone and aborted at less than 6 weeks; progesterone was not taken during any of these pregnancies. Two pregnancies (nos. 9 and 12) were treated with progesterone suppositories. Tissue from pregnancy no. 9, a SAB at 8 weeks, and pregnancy no. 12, a SAB at 16 weeks, was available for review. During pregnancy no. 12, an ultrasound at 9 weeks showed a subchorionic hematoma and a living fetus, but the MSAFP was elevated (2.7 MoM) at 14 weeks, and fetal death was diagnosed by ultrasound at 16 weeks.

Following the recognition of recurrent MCI (diagnosed initially in placenta 12, then retrospectively in placentas no. 3 and no. 6), pregnancy no. 13 was treated with immunosuppression by corticosteroids (20 mg prednisone daily from 6 weeks until delivery). The MSAFP was within normal limits. Serial ultrasounds showed normal amniotic fluid and normal fetal growth, but the umbilical artery Doppler assessment at 34 and 35 weeks became abnormal, with mildly decreased end diastolic flow. At 35 weeks' gestation, the patient ceased to feel fetal movement. Although the fetal testing was reassuring, a high risk for fetal compromise was present, and an amniocentesis was performed that documented fetal lung maturity. A 2,170-g (31st percentile) female infant (46,XX karyotype) was delivered by cesarean section because of breech presentation.

### Pathological Findings

**Pregnancy No. 3.** (SAB at 14 weeks). A 14-week male fetus (14-cm crown-rump length) had no congenital anomalies. Histologically, the placenta showed an intense mononuclear cell inflammatory infiltrate involving approximately 75% of the intervillous space, associated with numerous nodular aggregates of eosinophilic fibrin (Fig 1). Inflammatory cells were predominantly monocytes and histiocytes, with scattered lymphocytes. Villi were uninvolved by the chronic inflammation, and showed mild edema and fibrosis consistent with degenerative changes after fetal death.

**Pregnancy No. 6.** (SAB at 11 weeks). An autolyzed

### TABLE 1. Summary of Immunohistochemical Antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Titer</th>
<th>Specificity</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD45 (LCA)</td>
<td>1:20</td>
<td>All leukocytes</td>
<td>DAKO*</td>
</tr>
<tr>
<td>CD45RO (UCHL1)</td>
<td>1:400</td>
<td>T cells, monocytes, granulocytes</td>
<td>DAKO</td>
</tr>
<tr>
<td>L26</td>
<td>1:20</td>
<td>B cells</td>
<td>DAKO</td>
</tr>
<tr>
<td>CD68 (KP1)</td>
<td>1:50</td>
<td>Macrophages, monocytes</td>
<td>DAKO</td>
</tr>
<tr>
<td>HSV I</td>
<td>1:500</td>
<td>HSV I</td>
<td>DAKO</td>
</tr>
<tr>
<td>HSV II</td>
<td>1:200</td>
<td>HSV II</td>
<td>DAKO</td>
</tr>
<tr>
<td>CMV</td>
<td>1:100</td>
<td>CMV</td>
<td>DAKO</td>
</tr>
</tbody>
</table>

* Carpenteria, CA.

### TABLE 2. Summary of Pregnancies of Patient With Recurrent SAB

<table>
<thead>
<tr>
<th>Pregnancy No.</th>
<th>Year</th>
<th>Outcome/GA</th>
<th>Placental Pathology</th>
<th>Karyotype*</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1974</td>
<td>EAB 10 weeks</td>
<td>NA</td>
<td>—</td>
<td>Elective abortion</td>
</tr>
<tr>
<td>2</td>
<td>1979</td>
<td>SAB 11 weeks</td>
<td>NA</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>1986</td>
<td>SAB 14 weeks</td>
<td>Severe MCI; acute chorioamnionitis</td>
<td>—</td>
<td>Febrile; 14-week male fetus</td>
</tr>
<tr>
<td>4</td>
<td>1987</td>
<td>SAB 11 weeks</td>
<td>NA</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>1988</td>
<td>SAB 18 weeks</td>
<td>NA (possible MCI)†</td>
<td>—</td>
<td>Elevated MSAFP; 15-week fetus</td>
</tr>
<tr>
<td>6</td>
<td>1989</td>
<td>SAB 11 weeks</td>
<td>Severe MCI</td>
<td>46,XX</td>
<td>8.5-week embryo, progesterone; 2,900-g, healthy female infant</td>
</tr>
<tr>
<td>7</td>
<td>1990</td>
<td>SVD 41 weeks</td>
<td>NA</td>
<td>—</td>
<td>Elevated HCG</td>
</tr>
<tr>
<td>8</td>
<td>1991</td>
<td>SAB &lt;6 weeks</td>
<td>NA</td>
<td>—</td>
<td>Elevated HCG</td>
</tr>
<tr>
<td>9</td>
<td>1991</td>
<td>SAB 8 weeks</td>
<td>Necrotic villi</td>
<td>46,XX</td>
<td>Progesterone</td>
</tr>
<tr>
<td>10</td>
<td>1992</td>
<td>SAB &lt;6 weeks</td>
<td>NA</td>
<td>—</td>
<td>Elevated HCG</td>
</tr>
<tr>
<td>11</td>
<td>1992</td>
<td>SAB &lt;6 weeks</td>
<td>NA</td>
<td>—</td>
<td>Elevated HCG</td>
</tr>
<tr>
<td>12</td>
<td>1993</td>
<td>SAB 16 weeks</td>
<td>Severe MCI</td>
<td>46,XY</td>
<td>Progesterone; elevated MSAFP; 15-week male fetus</td>
</tr>
<tr>
<td>13</td>
<td>1994</td>
<td>C/S 35 weeks</td>
<td>Mild MCI</td>
<td>46,XX</td>
<td>Prednisone; 2,170-g, healthy female infant</td>
</tr>
</tbody>
</table>

Abbreviations: GA, gestational age; EAB, elective abortion; SAB, spontaneous abortion; MSAFP, maternal serum alpha-fetoprotein; MCI, massive chronic intervillositis; SVD, spontaneous vaginal delivery; C/S, cesarean section; NA, pathology slides not available for review.

* Patient and her husband also had normal karyotypes.

† Although pathological slide of pregnancy no. 5 were not available for review, the original placental pathological diagnosis (chorionic villi with extensive perivillous fibrin) suggests the possibility of MCI.
Embryo of 8.5 weeks' gestational age (1.3-cm crown-rump length) had a normal female karyotype (46,XX). Histologically, hyalinized placental villi were surrounded by abundant intervillous fibrin associated with a severe lymphohistiocytic chronic inflammatory infiltrate; approximately 50% of the intervillous space was involved by inflammation (Fig 2). No chronic villitis was present.

**Pregnancy No. 9.** (SAB at 8 weeks). Embryonic tissue was not identified. Placental histology showed necrotic immature villi with an unremarkable intervillous space, without chronic inflammatory cells. The karyotype was 46,XX; however, heteromorphic variants appeared similar to the mother's karyotype, raising the possibility of maternal cell (decidual) admixture.

**Pregnancy No. 12.** (SAB at 16 weeks). A 14-week, 49-g male fetus (46,XY) had no malformations; there was adrenal and thymic involution, consistent with...
chronic fetal stress. The placenta (48 g) had a marginally inserted umbilical cord. Histologically, there was massive infiltration of the intervillous space by mononuclear cells (predominantly histiocytes and lymphocytes), with abundant fibrin deposition; approximately 90% of the intervillous space was involved by the inflammatory process (Fig 3). The villous stroma was uninvolved by inflammation but showed focal hemorrhage and calcifications.

Pregnancy No. 13. (35-week cesarean delivery, immunosuppression with prednisone). The placenta (455 g) was grossly unremarkable. Histologically, a mild diffuse monocytic/histiocytic inflammatory infiltrate involved the intervillous space (Fig 4), significantly less intense than that of pregnancy nos. 3, 6, and 12; no significant intervillous fibrin deposition was present. Chronic villitis was not observed.

Immunohistochemistry

Placentas from pregnancy nos. 6, 12, and 13 were evaluated by immunohistochemistry. In all instances, the intervillous chronic inflammatory infiltrate was composed predominately of CD68 (Figs 3C and 4) and CD45 (LCA) immunoreactive cells, admixed with scattered CD45RO (UCHL1) positive cells (Fig 3D), consistent with a monocytic/macrophage population with scattered T lymphocytes. Only rare L26 positive cells (B lymphocytes) were noted. Scattered villous stromal cells also demonstrated CD68 staining, consistent with Hofbauer's cells. Placental CMV and HSV immunohistochemistry and stains for bacteria (Gram's and Stein er's stains) were negative.

DISCUSSION

Recurrent or habitual abortion (HAB), defined as three or more SABs before 20 weeks' gestational age, is estimated to affect 0.5% to 3% of couples. Although numerous causes have been proposed for HAB, only chromosomal disorders, uterine anomalies, and endocrine disturbances are well documented. The role of infection in HABs is unresolved, with the exception of lupus anticoagulant and antiphospholipid antibodies. In most couples with HAB (up to 70%), no cause is found, even after extensive medical investigation.

The role of the pathologist in the investigation of HAB is usually limited to the evaluation of luteal phase defect, diagnosed by a more than 48-hour delay in secretory endometrial maturation. Placentopathological changes in HAB have received little attention. Benirschke and Kaufman suggested that most HABs have no distinctive placental pathological features.

This article suggests that MCI may be a placental histopathologic diagnosis associated with HAB. Repetitive MCI associated with HAB has not previously been documented, although one prior patient with MCI had a history of HAB, systemic lupus erythematosus, and lupus anticoagulant. MCI in the first trimester has not previously been documented, with all prior reports involving late second- and early third-trimester placentas. Another novel feature of MCI reported here is a possible association between MCI and elevated MSAFP, found in two pregnancies ending in SAB at 16 and 18 weeks. Placental diagnoses previously associated with...
CHRONIC INTERVILLOSI-

FIGURE 4. Pregnancy no. 13, delivered at 35 weeks after maternal immunosuppression: Surrounding third-trimester villi, the intervillous space contains bland peri-
villous fibrin (A) and scat-
tered mononuclear in-
flammatory cells, which are
immunoreactive for CD68
(KP1), consistent with histio-
cytes/macrophages (A and
B: Immunohistochemistry for
CD68; original magnifica-
tions: A x200, B x400.)

The prevalence of MCI is not known, but it seems
to be a rare lesion, based on the 12 cases reported to
date.1,2 MCI is characterized histologically by extensive
chronic inflammation (macrophages/monocytes and
lymphocytes) located in the maternal intervillous space,
associated with intervillous fibrin deposition and vari-
able trophoblastic necrosis.1,2 In agreement with a previ-
ous report,2 our immunohistochemical studies showed
that the chronic inflammation of MCI is composed pre-
dominantly of monocytes/macrophages with scattered
T-lymphocytes. Previous reports have associated MCI
with other placental diagnoses, including focal mild
chronic villitis (in six of 12 reported cases), and mat-
ernal decidual vascular atherosis (in five of 12 reported
cases), but these placental diagnoses were not found in
this study. Clinical features previously associated with
MCI include maternal hypertension (in four of 12 re-
ported cases), fetal growth retardation (in six of 12
reported cases), fetal or neonatal death (in eight of 12
reported cases), and maternal systemic lupus crythema-
tosus (in two of 12 reported cases).

The cause of MCI is not known. Although an infec-
tious cause has not been entirely excluded, no prior
report has found evidence supporting an infectious
agent. An immunologic pathogenesis has been consid-
ered more likely,1,2 in part because of clinico-pathologic
similarities between MCI and chronic villitis of un-
known cause (CVUE), an idiopathic placental disorder
with a suspected immunologic pathogenesis.26-28

CVUE is a common placental pathological lesion
(prevalence 7.6% to 18% at term),20,28 strongly linked
to fetal growth retardation.26-31 CVUE is characterized
histologically by a villous lymphohistiocytic chronic in-
flammatory infiltrate, associated with destruction and
necrosis of the villous stoma and agglutination of in-
volved villi. The adjacent intervillous space in CVUE
may focially resemble MCI, with scattered foci of fibrin
deposition with a mononuclear cell inflammatory infl-
iterate (although this finding is often absent). It has been
noted that the intravillous chronic inflammatory cells
of CVUE are activated macrophages and antigen-pre-
senting helper T lymphocytes.26,31 Recently, the chronic
inflammatory cells of CVUE have been shown to be
maternal in origin,27 leading to the hypothesis that
CVUE may represent a maternal allograft rejection of fet-
tissues.25,27 The observations that CVUE may recur
in subsequent gestations and that CVUE is associated
with markers of maternal autoimmunity also support
a proposed immunologic pathogenesis.20 Redline and
Abramowsky20 noted an 18% recurrence rate in CVUE,
and noted that recurrent CVUE is associated with evi-
dence of autoimmunity, severe fetal growth retardation,
and previous abortions. CVUE has also been associated
with elevated MSAFP.

Because of the many clinical and histopathologic
similarities between MCI and CVUE, Labarrere and
Mullen1 suggested that MCI might represent an un-
usual variant of CVUE, with a similar immunologic
pathogenesis. The presence of a similar population of
maternal chronic inflammatory cells in both conditions
further supports this hypothesis.2,26,27,31 The clinico-
pathologic resemblance of MCI to CVUE is further
strengthened by this report, which shows that MCI, like
CVUE, may be a repetitive placental cause of recurrent
pregnancy loss associated with an elevated MSAFP.

An additional placental pathological disorder that
shares some clinical and pathological features with MCI
is maternal floor infarct (MFI).21,32-35 MFI is a rare,
poorly understood, idiopathic placental lesion (preva-
ience .09% to .5% at term),32,35 which is highly linked
with fetal growth retardation and recurrence. MFI has also been associated with elevated MSAFP. MFI is grossly characterized by a plaque-like thickening of the maternal surface of the placenta. Histologically, there is extensive deposition of fibrin in the basal maternal intervillous space and the decidua basalis, with entrapment of sclerotic basal villi by fibrin; the intervillous fibrin of MFI is not associated with chronic inflammation. Although the pathogenesis of MFI is not established, Benirschke and Kaufman suggested that it may be related to an abnormal host-placental interaction. Other proposals for the pathogenesis of MFI include recurrent latent HSV infection, and intermediate trophoblast (X-cell) production of major basic protein. A final interesting feature of this report is the possible association of MCI and "embryotoxic factors." Embryotoxic factors have been proposed as a new immunologic cause for recurrent abortion based on TH1-type immunity to trophoblast. These TH1-type cytokines interferon-gamma and tumor necrosis factor have been reported to inhibit embryonic development, and trophoblastic growth and function. These antitrophoblastic cytokines have been associated with unexplained recurrent SAB and have been reported to be inhibited with immunosuppressive doses of progesterone. This study suggests that placental MCI may be a histopathologic correlate of TH1-type antitrophoblastic immunity in patients with recurrent abortion. More immunopathologic studies are needed to confirm this possible association and to discern potential cause versus effect phenomena.

In conclusion, the authors report repetitive placental MCI in four of five gestations from a patient with 10 SABs. Maternal immunosuppression with corticosteroids during the most recent gestation resulted in mild placental MCI associated with a successful pregnancy outcome. This suggests that recurrent placental MCI may be a histopathologically recognizable cause for HAB, which is amenable to therapeutic intervention. Clinicopathologic similarities between MCI and CVUE (maternal histiocyties and T lymphocytes; fetal growth retardation; maternal autoimmunity; recurrence; and elevated MSAFP) support the concept that MCI and CVUE may be related placental disorders that share similar immunologic pathogenesises.

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