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Phenotype of Villous Stromal Cells in Placentas with Cytomegalovirus, Syphilis, and Nonspecific Villitis

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Villous stromal cells (VSC) play an important role in fetomaternal placental immune function. We studied the phenotype of VSC in infection by cytomegalovirus (CMV) and syphilis as well as nonspecific villitis and compared the findings with gestational age-matched controls. Monoclonal antibodies directed against total leukocytes, T cells, B cells, macrophages, dendritic cells, granulocytes and HLA-DR as well as polyclonal antibodies against S-100, alpha-1 antichymotrypsin, and lysozyme were used. In controls, the immunocytochemical response for each marker was either negative or weakly positive. In contrast, the VSC in CMV-infected and nonspecific villitis showed intense reactivity to various macrophage markers. In syphilis, reactivity with macrophage markers such as lysozyme and MAC387 were weaker, and reactivity to HLA-DR and S-100 was much stronger. Endothelial cells strongly expressed the monocyte/granulocyte marker CD15 in the diseased states, especially in syphilis, relative to controls. We conclude that the phenotype of VSC is altered in disease states and that the changes are dependent to some degree on the specific subset of chronic villitis. (Am J Pathol 1992, 141:835–842).

Villous stromal cells (VSC) are believed to play an important role in fetomaternal placental immune function. These mesenchymal villous cells consist of fixed stromal cells and macrophages that are abundant throughout gestation. In contrast, T and B lymphocytes are scarce in the normal placental villous at all times.[1] Villous stromal cells together with lymphocytes and neutrophils are increased in various proportions in different types of villitis.[2–4] The antigenic phenotype of VSC has been previously studied in normal placentas and in a few pathologic conditions.[1,5–13] The current study compares the phenotype of VSC in different types of chronic villitis and shows the possible association of specific phenotypic expression with various pathologic conditions.

Materials and Methods

Twenty-one cases of chronic villitis were obtained from the files of the pathology departments at New York University Medical Center, Harlem Hospital Medical Center, and University Hospital at Stony Brook. These cases included seven of cytomegalovirus (CMV) infection and five of syphilis. Nine cases were classified as nonspecific chronic villitis after special stains for bacteria, fungi, treponema, and acid-fast organisms and *in situ* hybridization for CMV-DNA on placental tissue were negative. These placentas were compared with 19 histologically normal placentas of uncomplicated deliveries matched for gestational age ± 2 weeks. In addition, three full-term placentas from human immunodeficiency virus (HIV)-positive women and three third-trimester placentas from mothers with gestational diabetes without villitis were also studied. The cases of gestational diabetes served as control for the cases of syphilis, because both tend to show histologically immature villi for gestational age. This enabled us to study whether the stromal changes were related to infection or to immaturity.

The clinical data are summarized in Tables 1, 2 and 3. Cases 1 and 4 through 7 of Table 1 and cases 7 and 9 of Table 3 have been the subject of a previous report, and

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Table 1. *Clinical Data Chronic Villitis: CMV*

Case	Weight (g)/Sex/ Gestation (wk)	Serology/ Cultures	Other data
1	430/female/21	ND	Stillborn
2	770/female/29	CMV 1:4† HSV 1:2†	Hydrops fetalis, cardiomegaly, anemia, petechiae, hydrocephalus; died at day 3
3	1174/male/31	CMV 1:4*	Intrauterine growth retardation, anemia, thrombocytopenia, staphylococcal sepsis; died at 1 month
4	1590/male/32	ND	Stillborn
5	2545/male/32	ND	Thrombocytopenia, petechiae, ascites, hepatosplenomegaly; died at day 3
6	3175/female/40	Negative	Well baby
7	3110/male/42	CMV 1:128† HSV 1:128† Rubella 1:64† Toxo(−)†	Born alive; petechiae, thrombocytopenia, splenomegaly

* Maternal.
† Infant.
ND = not done, CMV = cytomegalovirus, HSV = Herpesvirus, Toxo = toxoplasma, GI = gastrointestinal.

detailed clinical data are given in reference 14. There were eight stillbirths, four neonatal deaths, and nine neonates who survived. Seven stillborn and three neonates came to autopsy. The maternal ages ranged from 17 to 36 years. There was a history of maternal hypertension in cases 2 and 6 (Table 1) and cases 1 and 8 (Table 3). Gestational diabetes was present in case 1 and autoimmune thrombocytopenia in case 3 (Table 3). Two women with syphilis also were cocaine dependent (cases 3 and 5). The diagnosis of CMV villitis was confirmed in all cases by *in situ* hybridization of the placenta using a methodology previously published.[14] All cases of syphilis had serologic confirmation and in two instances, spirochetes were found in the placentas. Among the nonspecific villitis cases, one mother had measles (case 2), one had elevated human parvovirus B 19 titers (case 6,) but no viral inclusions were identified in any of the infant's organs, and one (case 8) had varicella with the stillborn fetus showing microscopic hepatic and pulmonary calcification. A maternal history of two previous infants with intrauterine growth retardation and villitis of unknown origin was present in case 4 (Table 3).

Gross examination of the placentas was done according to a standard protocol.[15] Four to six sections from each placenta, including the chorionic and decidual plates, were analyzed histologically after fixation in 10% buffered formalin. Sections 4 microns thick were studied with routine hematoxylin and eosin (H&E) stain. Selected tissues were stained for hemosiderin pigment, bacteria, acid-fast bacilli, fungi, and spirochetes.

Villous areas showing chronic villitis were selected for immunocytochemical studies. The mouse monoclonal and rabbit polyclonal antibodies used in this study are listed in Table 4. A three-step avidin-biotin immunoperoxidase technique using Fisher Code-On automated stainer as described by Brigati et al,[16] was used, with the following modifications: the secondary antibody and avidin-biotin detection system was either the mouse IgG or the rabbit IgG Vectastain ABC Elite kit (Vector Laboratories, Burlingame, CA), Incubation times were as follows: primary antibody, 60 minutes; secondary antibody, 25 minutes; ABC elite complex, 25 minutes. All were performed at 37°C. The chromogen was 3-3′ diaminobenzidine incubated for 10 minutes at 37°C used according to manufacture's directions (Kirkegaard Perry Laboratories, Rockville, MD). Sections to be stained with MAC387, and CD68 (KP1) required a 20-minute digestion with autozyme (Biomeda, Foster City, CA) before application of the primary antibody. Negative controls consisted of replacing the primary antibody with the appropriate dilution of mouse or rabbit immunoglobulins (Biogenex, San Ramon, CA). Positive control tissue consisted of tonsil or

Table 2. *Clinical Data Chronic Villitis: Syphilis*

Case	Weight (g)/Sex Gestation (wk)	Serology/Cultures*	Other data
1	90/male/19	VDRL 1:16, FTA (ABS) reactive	Stillborn, maceration
2	1900/male/31	VDRL 1:32, FTA (ABS) reactive	Stillborn, osteochondritis, maceration
3	1950/female/36	VDRL 1:64, FTA (ABS) ND	Stillborn, maceration
4	2860/male/39	VDRL 1:512, FTA (ABS) reactive	Born alive, congenital syphilis, treated
5	3120/male/40	VDRL 1:128, FTA (ABS) reactive	Born alive, congenital syphilis, treated

* Maternal.
ND = not done.

Table 3. *Clinical Data Nonspecific Villitis*

Case	Weight (g)/Sex/ Gestation/(wk)	Serology/ Cultures	Other data
1	435/female/21	ND*	Stillborn, maceration
2	1515/male/28	(−)†	Born alive, respiratory distress
3	670/female/30	ND*	Stillborn, intrauterine growth retardation, maceration
4	1550/male/36	(−)†	Intrauterine growth retardation discharged home at 1 month
5	1575/female/36	(−)†	Born alive, intrauterine growth retardation
6	2300/female/36	HPV-B19, IgG(+)†	Fetal bradycardia & heart block, hydrops fetalis, asplenia-polysplenia syndrome, died at day 2
7	3381/male/36	ND†	Well baby
8	2100/male/37	CMV(+)†Toxo(−)† HSV(+)†	Intrauterine growth retardation, hydrocele, recurrent colds
9	3420/female/42	ND*	Stillborn, simian crease of right hand

* Maternal.
† Infant.
ND = not done, HPV = Human parvovirus, Toxo = Toxoplasma, CMV = Cytomegalovirus, HSV = herpesvirus

lymph node. The numbers of positive VSC in each case were evaluated for each antibody tested by three independent observers (MAG, RW, RS). The results were averaged and graded as follows: ± for 1 to 5 cells per 5 high-power fields (HPF), 1+ for 5 to 25 cells per HPF, 2+ for 25 to 50 cells per HPF, and 3+ for more than 50 cells per HPF. The predominant average grade for each antibody in each category (controls, CMV villitis, nonspecific villitis, and syphilis) was chosen (see Tables 5 and 6).

Results

Gross and Microscopic Pathology

The placentas varied in weight from 140 to 980 g. Five CMV, one syphilitic, and one of the nonspecific villitis placentas were small compared with control placentas of the same gestational age.[17] Five placentas were heavier, one each with CMV and nonspecific villitis, one with syphilis, and two diabetic cases. In one syphilitic placenta the weight was not recorded.

Chronic villitis with a mixed mononuclear infiltrate composed of lymphocytes, plasma cells, histiocytes (including Hofbauer cells) and fibroblasts was noted in 16 cases. Detailed histologic descriptions of cases 1 and 4 through 7 of CMV and 7 and 9 of nonspecific villitis have been previously reported.[14] The additional cases of CMV and nonspecific villitis showed similar findings to those previously described.[2,3] The CMV villitis in the current cases was also similarly associated with deposition of hemosiderin pigment and typical intranuclear inclusions. The cases of nonspecific villitis also showed a mixed mononuclear infiltrate but with a predominance of histio-

Table 4. *Antibodies Used in This Study*

Antibody	Specificity	Source	Titers
CD45* (LCA)	All leukocytes	DAKO‡	1:100
HLA-DR* (LN3)	Monocytes, Macrophages, B cells, Dendritic cells, Activated T cells	ICN Biomedical‖	1:20
CD68* (KP1)	Macrophages, Monocytes, Granulocytes (weak)	DAKO‡	1:100
CD15* (Leu M1)	Monocytes, Granulocytes, Activated T cells, Reed-Sternberg cells	Becton-Dickinson¶	1:50
MAC 387*	Macrophages, Monocytes, Not GC macrophages Dendritic cells	DAKO‡	1:300
L-26*	B cells	DAKO‡	1:200
CD45RO* (UCHL1)	T cells, Monocytes, Granulocytes	DAKO‡	1:200
S-100†	Langerhans cells, Interdigitating dendritic cells, Some T cells	DAKO‡	1:1000
ACT†	Histiocytes, Granulocytes (+/−)	DAKO‡	1:25,000
LYS†	Histiocytes, Granulocytes	DAKO‡	1:5,000

* Monoclonal.
† Polyclonal.
‡ Carpenteria, CA.
‖ Costa Mesa, CA.
¶ Mountain View, CA.
GC: germinal center, ACT: alpha-1-antichymotrypsin, LYS: Lysozyme
See text for all other abbreviations.

Table 5. *Phenotype of Villous Stromal Cells*

	No. cases	CD45 (LCA)	HLA-DR (LN3)	CD68 (KP1)	S-100	ACT	MAC 387	LYS	L-26	CD45RO (UCHL1)
2nd tri controls	5	1+	+/−†	1+	1+	+/−	−	−	−	−
3rd tri controls	14	+/−	+/−†	+/−	+/−	+/−	−	−	−	−
CMV*	6	2+	1+	2+	1+	1+	2+	2+	−	−
Syphilis	4	3+	3+	2+	3+	1+	+/−	+/−	−	−
Nonspecific*	8	2+	1+	2+	1+	1+	2+	2+	−	−

* In areas of villitis and intervillositis.
† Rare positive cell in fibrin.
Tri: trimester. See text for other abbreviations.

cytes. Two of these cases (cases 1 and 8, Table 3) showed giant cells and a granulomatous reaction. In one case with granulomatous reaction (case 8), there was a maternal history of varicella. Intervillositis with a predominance of mononuclear cells was prominent in one case each of CMV (case 2) and nonspecific villitis (case 3).

Four cases of syphilis (cases 1 through 4, Table 2) showed increased histiocytes and Hofbauer cells in addition to a few plasma cells and lymphocytes. Two cases (cases 1 and 5) showed necrosis and agglutination of villi with intervillous fibrin and granulocytes. All cases of syphilis showed variable degrees of villous fibrosis and sclerosis and obliteration of blood vessels. Spirochetes were seen in two syphilitic placentas (cases 2 and 5). Extramedullary hematopoiesis was noted in three cases of syphilis (cases 2, 3, and 5) and in one case each of CMV (case 2) and nonspecific villitis (case 3).

Inflammation of the decidua was variable, but when present it was focal with focal necrosis. Chronic inflammation was seen in two CMV cases (case 2 and 3), two cases of syphilis (cases 1 and 5), and in two cases of nonspecific villitis (cases 1 and 4). Acute deciduitis was present in two cases of syphilis (cases 1 and 3) and both acute and chronic in one case of syphilis (case 2) and in two cases of nonspecific villitis (cases 3 and 8). Acute chorionitis or chorioamnionitis was seen in all five cases of syphilis, in one CMV case (case 1), and in two cases of nonspecific villitis (cases 3 and 9). Acute funisitis was present in four syphilitic placentas. The placentas from HIV-positive women showed no significant villous pathology, but all three had acute inflammation of the fetal membranes without involvement of the umbilical cord. The three placentas from women with gestational diabetes showed immaturity of the villi without inflammation. The membranes and umbilical cords were unremarkable.

Immunocytochemistry

The results of the immunocytochemical studies are summarized in Tables 5 and 6.

The control cases showed a few positive VSC for CD45, CD68, CD15, S-100 and alpha-1-ACT antigens. MAC387, LYS, L-26, and CD45RO were negative. There was a modest increase in positive VSC in the second trimester for CD45, CD68, and S-100 antigens. Human leukocyte antigen (HLA-DR) was weakly positive in occasional VSC and in all placentas without much variation at different gestational ages. CD15 was focally expressed in endothelial cells of villous capillaries in 10 of 19 control cases (Table 6). There were no staining differences between normal third-trimester placentas, the placentas of HIV-positive mothers, or the gestational diabetes placentas.

Comparing with third trimester controls, the 14 third trimester cases of CMV and nonspecific villitis (Table 5) showed a moderate increase in positive VSC for HLA-DR, S-100, and alpha-1-ACT antigens. There was a marked increase in positive VSC in the cases of CMV and nonspecific villitis *versus* controls for CD45. CD68, MAC387, LYS, and ACT antigens were strongly expressed in the VSC of villitis and in cells of the intervillositis (Figure 1). The remaining VSC showed variable expression. Expression of HLA-DR was also variable but stronger in more cases of nonspecific villitis than CMV villitis (Table 5). Four of the syphilitic placentas (cases 2 through 5) showed a different pattern of cell marker ex-

Table 6. *CD15 (Leu M1) Expression in Villous Endothelium*

Placentas	Positive cases/ Total cases	Range of positive cells
Control second trimester	4/4 (100%)	+/− to 1+
Control third trimester	6/15 (40%)	+/− to 1+
CMV	7/7 (100%)	+/− to 3+
Syphilis	4/4* (100%)	2–3+
Nonspecific	7/9 (78%)	− to 3+
Diabetes mellitus	1/3 (33%)	− to +/−

* Third trimester.

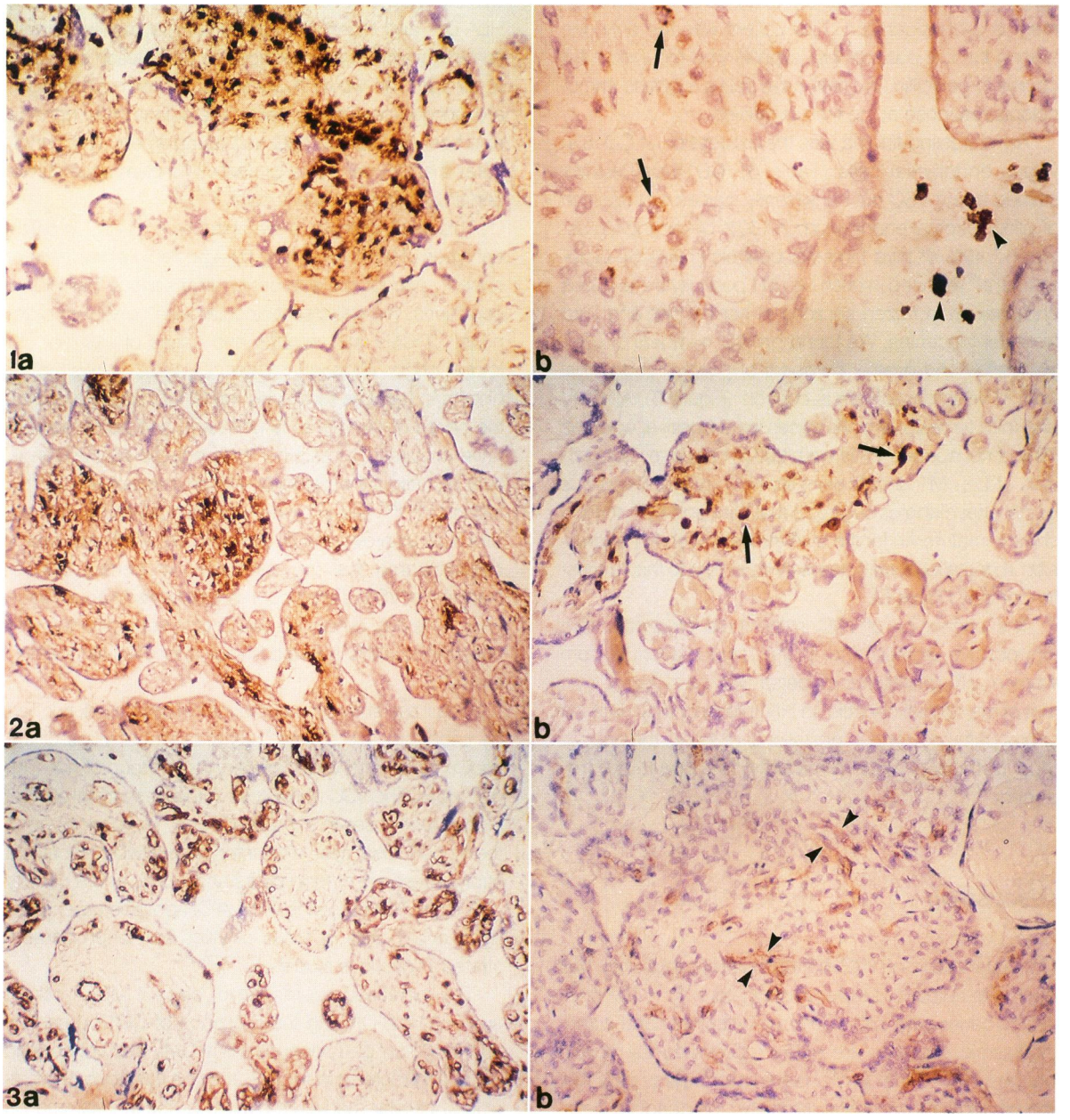

Figure 1. a, b: *CD68 (KP1) antigen is strongly expressed in VSC in an area of villitis* **(a).** *Compare this case of nonspecific villitis with a normal control placenta in which only occasional cells are positive (arrows)* **(b).** *Note positive circulating maternal cells (arrowheads)* **(b).** *DAB with hematoxylin counterstain.* **a:** *×50;* **b:** *×100.*
Figure 2. a, b: *S-100 antigen is strongly expressed in VSC of a syphilitic placenta* **(a).** *Fewer S-100 positive cells are seen in a normal control placenta (arrows)* **(b).** *DAB with hematoxylin counterstain.* **a:** *×25;* **b:** *×50.*
Figure 3. a, b: *A syphilitic placenta shows stronger expression of CD15 (LeuM1) in villous endothelium* **(a)** *compared with a normal control histologically immature placenta (arrowheads)* **(b).** *Note fibrosis of the villi in the syphilitic placenta* **(a).** *DAB with hematoxylin counterstain.* **a:** *×25;* **b:** *×50.*

pression. CD45, HLA-DR, and S-100 antigens were strongly expressed in all VSC (Figure 2) and MAC387 and LYS had rare positive cells. L-26 was not found on VSC. CD45RO occasionally showed faint VSC positivity, which we thought was background staining. Occasional L-26 positive B cells were found in syphilis; however, most lymphocytes in villitis were CD45RO positive T cells.

The one second trimester case of CMV villitis and the second trimester case of nonspecific villitis were similar in phenotype to their third trimester counterparts. The second trimester syphilitic placenta, however, showed a pattern of antigen expression more similar, albeit weaker, to nonspecific villitis than to the third trimester syphilitic cases. In this case, the mother was treated and the pos-

sibility of an unusual, modified response due to the treatment is a consideration. This patient was the only one among the five patients with syphilis who received a full course of penicillin and may have had a modified immunologic response at the time of delivery.

An interesting finding was the expression of CD15 in villous endothelial cells (Table 6). CD15 or Leu M1 stained a rare VSC but consistently stained a proportion of villous stromal endothelium in 100% of second trimester and 40% of third trimester controls (Table 6). Goldstein et al[8] reported intense Leu M1 positivity of the villous endothelium in frozen sections of normal first and third trimester placentas. We found greater numbers of positive cases and greater numbers of positive endothelial cells in villitis cases versus controls (Figure 3). All CMV and third trimester syphilis cases were positive, whereas 78% of nonspecific villitis were Leu M1 positive. Comparison of Leu M1 endothelium staining in syphilis *versus* gestational diabetes suggests that although both tend to show immature villi for the third trimester, Leu M1 expression in gestational diabetes is more similar to third trimester controls (Table 6).

The phenotype of VSC in the three placentas from HIV-positive women and in the three placentas from women with gestational diabetes was no different from that of the normal controls. In HIV infection, there was no villous pathology and in gestational diabetes the only villous pathology was immaturity, as previously reported.[18,19]

Discussion

Characterization of VSC during normal pregnancy has been attempted by several investigators.[1,5–11] The classic Hofbauer cells with abundant cytoplasm and intracytoplasmic vacuoles are easily recognized as macrophages.[1,20,21] Other similar but smaller cells or cells that morphologically resemble fibroblast or dendritic cells, however, have been found to express monocyte-macrophage markers.[1,8] The proportion of these cells and their expression of cell markers related to immunologic functions vary with gestational age.[1,8]

Nakamura et al[1] found immunoreactivity with HLA-ABC in almost all VSC throughout pregnancy; however, only a few VSC were positive for HLA-DR in the first trimester. Their number increased in the second and third trimester. LCA and CD4 were positive in about half of the VSC throughout pregnancy. Markers for monocyte/macrophages lineage such as Leu-M3, Leu-M5, Mac-1, ATC, and S-100 protein were positive in VSC, particularly during the second and third trimesters.[1] Goldstein et al[8] detected class II histocompatibility antigens HLA-DR, HLA-DP, and HLA-DQ in placental macrophages, with some variation in their expression as function of gestational age. This would suggest that villous macrophages are antigen-presenting cells. The villous macrophage also has receptors for IgG and complement, which indicates that this cell has a protective function against maternal antibodies to fetal tissues.[8,11,22]

This study compares the phenotype of VSC in different types of villitis searching for a possible association of specific phenotypic expression and various pathologic conditions. We selected placentas with confirmed diagnoses of CMV and syphilis and cases of villitis of unknown origin. Although nonspecific villitis shows similar histologic features to chronic villitis with specific cause, the cause of the former is unknown, and some authors have proposed a maternal immunologic aggression to fetal tissues as the pathophysiologic mechanism for this lesion.[12,23–25] Our immunocytochemical study can not prove or disprove this hypothesis, but we have clearly demonstrated that the expression of certain cellular markers for VSC is identical in both CMV and nonspecific villitis. The only difference was that fewer placentas with nonspecific villitis showed villous endothelium positivity for CD15.

One case showed marked intervillositis as described by Labarrere and Mullen[26] as a variant of villitis of unknown cause and was included in our group of nonspecific villitis. The VSC phenotype in this case parallels that of the other cases in the same group. The phenotype of the mononuclear cells in the intervillous space indicates a strong presence of monocytes and T cells and a paucity of B cells. The presence of HLA-DR-positive machrophages and T-cells in areas of villitis has been demonstrated in previous studies.[12,13,27–29]

The increased expression of class II MHC antigen such as HLA-DR and the presence of CD15 (Leu M1) and S-100 antigen positive cells in CMV and nonspecific villitis, and more so in syphilis, may be related to the stimulus of cellular mediators playing a role in inflammation and immunity. It has been demonstrated in culture of umbilical vein and foreskin microvascular endothelium that gamma interferon induces the expression of HLA-DR on the surface of these endothelial cells.[30] Cytokines and endotoxin also cause increased expression of other antigens such as ICAM-1 (intercellular adhesions molecule 1), an antigen that is involved in lymphocyte -endothelial interactions.[31,32] ICAM-1 has been identified in VSC after 14–16 weeks gestation in normal placentas[33] but its presence in villous capillaries is unknown.

The increased expression of CD15 or Leu M1 in villous endothelial cells of placentas with villitis especially in third trimester syphilis may also be related to the in-

creased expression of ELAM-1 which has been demonstrated in activated endothelium.[31,32] ELAM-1 recognizes a form of the Leu M1 antigen on granulocytes.[34] Perhaps CD15 or LeuM1 may act as some sort of cellular adhesion molecule in normal placentas which is up regulated in chronic inflammation. Increased expression of other antigens, such as class II MHC antigens, in villous endothelium in cases of villitis has been reported by Labarrere et al.[29]

In summary, it is clear that the phenotype of VSC changes in response to or as a consequence of infection or chronic inflammation, although no cellular markers unique to a specific type of villitis could be ascertained. Nevertheless a somewhat different pattern of antigen expression was observed in third trimester syphilitic placentas, pointing to a different type of immunologic response of placental tissue to the treponema when compared with CMV and nonspecific villitis.

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