Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance

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Chronic inflammatory lesions of the placenta are characterized by the infiltration of the organ by lymphocytes, plasma cells, and/or macrophages and may result from infections (viral, bacterial, parasitic) or be of immune origin (maternal anti-fetal rejection). The 3 major lesions are villitis (when the inflammatory process affects the villous tree), chronic chorioamnionitis (which affects the chorioamniotic membranes), and chronic deciduitis (which involves the decidua basalis). Maternal cellular infiltration is a common feature of the lesions. Villitis of unknown etiology (VUE) is a destructive villous inflammatory lesion that is characterized by the infiltration of maternal T cells (CD8+ cytotoxic T cells) into chorionic villi. Migration of maternal T cells into the villi is driven by the production of T-cell chemokines in the affected villi. Activation of macrophages in the villi has been implicated in the destruction of the villous architecture. VUE has been reported in association with preterm and term fetal growth restriction, preeclampsia, fetal death, and preterm labor. Infants whose placentas have VUE are at risk for death and abnormal neurodevelopmental outcome at the age of 2 years. Chronic chorioamnionitis is the most common lesion in late spontaneous preterm birth and is characterized by the infiltration of maternal CD8+ T cells into the chorioamniotic membranes. These cytotoxic T cells can induce trophoblast apoptosis and damage the fetal membranes. The lesion frequently is accompanied by VUE. Chronic deciduitis consists of the presence of lymphocytes or plasma cells in the basal plate of the placenta. This lesion is more common in pregnancies that result from egg donation and has been reported in a subset of patients with premature labor. Chronic placental inflammatory lesions can be due to maternal anti-fetal rejection, a process associated with the development of a novel form of fetal systemic inflammatory response. The syndrome is characterized by an elevation of the fetal plasma T-cell chemokine. The evidence that maternal anti-fetal rejection underlies the pathogenesis of many chronic inflammatory lesions of the placenta is reviewed. This article includes figures and histologic examples of all chronic inflammatory lesions of the placenta.

Key words: allograft, C4d, CD8, chemokine, chronic chorioamnionitis, chronic deciduitis, complement, CXCL10, fetal death, fetal growth restriction, HLA, maternal floor infarction, plasma cells, prematurity, rejection, T cell, tolerance, VUE

The term *chronic inflammation* refers to a pathologic process that is characterized by the infiltration of lymphocytes, plasma cells, and histiocytes (ie, tissue macrophages).[1] Chronic placental inflammatory lesions can be present in the villous tree, extraplacental chorioamniotic membranes, chorionic plate, and basal plate of the placenta (Figure 1). Identification of the causes of chronic inflammatory lesions of the placenta is an important challenge.[2-4] Infection[5-7] due to viruses,[8-12] bacteria (ie, *Treponema pallidum, Mycobacterium tuberculosis*),[11,13] or parasites (ie, *Plasmodium spp., Toxoplasma gondii*)[8] has been implicated; however, most chronic inflammatory lesions are of unknown cause (ie, an infectious agent cannot be identified),[14] and accumulating evidence suggests that an immune process caused by maternal anti-fetal rejection plays a role in the pathogenesis of these conditions.[4,15-24]

The placenta and fetus are semiallografts; a maternal (host) immune response against paternal antigens (expressed in the placenta or fetus) can be considered analogous to allograft rejection.[25-34] We will review the evidence in support of the concept that many cases of idiopathic chronic placental inflammation reflect maternal anti-fetal rejection, in which the main effector is the infiltration of maternal CD8+ T cells (cytotoxic lymphocytes) into fetal tissues (Figure 2).[15,16,35] This state is associated with the presence of fetal human leukocyte antigen (HLA)-specific antibodies in the maternal serum,[17,18,21] C4d deposition in the umbilical vein,[17,22] and the syncytiotrophoblast.[24] The presence of fetal HLA-specific antibodies in maternal serum was first determined by the performance of HLA genotyping

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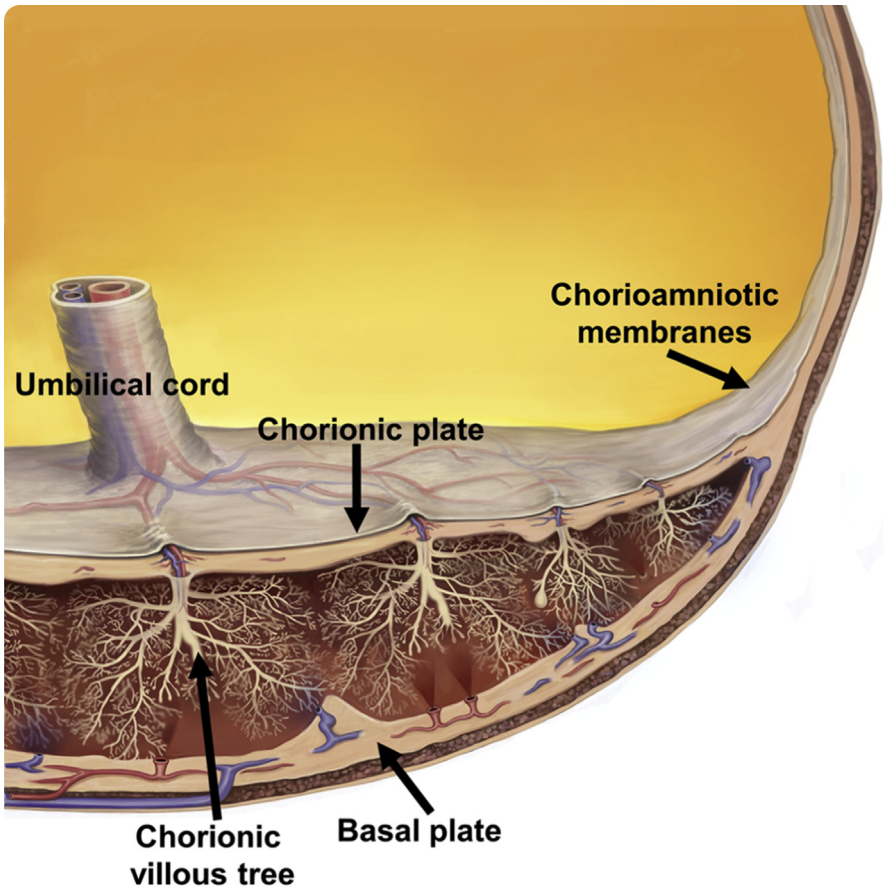
FIGURE 1
The human placenta



Chronic inflammatory lesions can affect different parts of the placenta. Chronic villitis refers to the inflammation involving the villous tree. Chronic chorioamnionitis involves either the extraplacental chorioamniotic membranes or chorionic plate. Chronic deciduitis affects the basal plate.

Modified from Benirschke K, Burton GJ, Baergen RN, editors. Infectious diseases. In: Pathology of the human placenta. 6th ed. Berlin: Springer; 2012:557-656.

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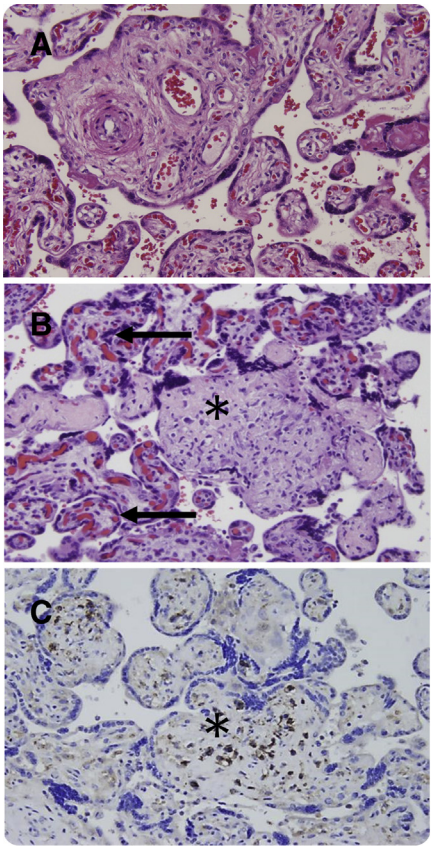
FIGURE 2
Microscopic findings of chronic nonspecific villitis of unknown etiology



A, Normal chorionic villi showing the villous core with fetal vessels and stroma. The intervillous space contains maternal red blood cells. The rest of the image shows cross-sections of the villous tree of the placenta; each chorionic villus is lined with syncytiotrophoblast. Inside the villi, fetal capillaries are observed. **B,** Destructive inflammation of the chorionic villus (*asterisk*). The inflammatory process is diagnosed by the presence of an infiltration of mononuclear cells. Obliteration of the villous capillaries is also seen in comparison to unaffected villi adjacent to the distorted villus (*asterisk*). Unaffected villi (*black arrow*). **C,** Destructive inflammation of the chorionic villi (asterisk) Immunoperoxidase staining for CD8+ T cells. Cells stained in brown express CD8 on their surface and are therefore cytotoxic lymphocytes. These cells are of maternal origin, and are derived from the intervillous space. Original magnification (**A-C**), 200×.

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with the use of fetal genomic DNA and then the assessment of whether the maternal HLA antibodies were directed against fetal antigens with the use of a Luminex assay (Life Technologies, Rockville, MD).[18,21] Furthermore, the concentrations of T-cell chemokine CXCL10 are elevated in different fetal compartments, such as the amniotic fluid and fetal plasma.[15,16,20] These phenomena resemble those that are observed in allograft rejection in solid organ transplantation.[36-49]

Chronic nonspecific villitis

Definition and cellular composition

Villitis of unknown etiology (VUE) is a destructive inflammatory lesion characterized by the infiltration of maternal T cells into the chorionic villi (fetal tissue).[50,51] The frequency of VUE varies among studies, and its prevalence ranges from 2-33.8%.[7,52-56] The wide range is thought to represent variations in the study population, sampling methods, and diagnostic criteria. The frequency of detection of VUE increases when the number of paraffin blocks from a given placenta increases to 4.[52]

The main maternal T-cell subset infiltrating the chorionic villi is CD8+ cytotoxic T cells.[35] The maternal origin of these T cells was demonstrated by Redline and Patterson[50] who used in situ hybridization analysis with X and Y