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The immunological basis of villitis of unknown etiology – Review

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ABSTRACT

Villitis of unknown etiology (VUE) represents a common placental inflammatory lesion, primarily, but not exclusively, identifiable T lymphocytes at term. Despite considerable evidence to contest that this simply represents a benign pathological finding, VUE remains a significantly undervalued diagnosis. Given its association with adverse pregnancy outcomes; including fetal growth restriction, preterm birth, and recurrent pregnancy loss, an increased awareness amongst clinician obstetricians is certainly warranted.

The underlying immunopathogenesis of VUE remains uncertain. Despite initial theories that this represents an infectious placental lesion of undiagnosed pathogenic source, a more complex sequence of events involving the "breakdown" of maternal–fetal tolerance is emerging. Characterization of a unique inflammatory phenomenon in which both maternal and fetal T lymphocytes and Höfbauer cells interact has captivated particular research interest and has generated analogies to both the problems of allograft rejection and graft-versus-host disease (GvHD).

Within the context of VUE, this review evaluates how disruption of the multidimensional immunological mechanisms underlying feto-maternal tolerance may permit abnormal lymphocyte infiltration into placental villi. We shall review the existing evidence for these events in VUE and outline areas of certain future interest.

1. Introduction

Villitis of unknown etiology (VUE) is one of the most common, inflammatory placental lesions [1,2]. Albeit visualized at any gestation, its incidence is higher at term [2]. Histologically, VUE is characterized by an "inflammatory cell infiltrate", containing Höfbauer cells (placental macrophages) and T-cell lymphocytes within the placental villi, in the absence of an infective etiology [3]. The placental pathology was first recognized in the 1960's by Gershon and Strauss [4], but not until 1975 was VUE defined and differentiated pathologically from placental lesions of a known infective source [5]. Even today, VUE remains a placental enigma and its importance is significantly under recognized due in part to a lack of awareness amongst clinicians. This review will describe our current understanding of VUE, its clinical consequences, and the most current hypotheses regarding its true underlying etiology.

2. Background

VUE is a solely histopathological diagnosis which can further be classified according to distinct patterns of trophoblast villous involvement (Fig. 1b–d). The predominant diagnostic feature of VUE is simply an inflammatory cell infiltrate, characterized by mononuclear cells and areas of destructive fibrinoid necrosis, within the substance of the chorionic villi in the absence of an identifiable infectious agent [5–9]. Unlike villitis of infectious origin, a cardinal feature is the non-uniform involvement of the placental parenchyma, with unaffected portions most often maintaining their normal histological architecture [2]. The most common pattern (>50%) reported remains localized to distal villi with sparing of the chorionic plate, proximal stem villi, and anchoring villi embedded in the basal plate (Fig. 1b). In approximately 30%

Abbreviations: Villitis of unknown etiology, VUE; T regulatory cells, TReg cells; major histocompatibility complex, MHC; pre-term labor, PTL; intra-uterine growth restriction, IUGR; small for gestational age, SGA; cerebral palsy, CP; neurological impairment, NI; body mass index, BMI; systemic lupus erythematosis, SLE; in vitro fertilization, IVF; antibody, Ab; natural killer, NK; interferon-γ, IFNγ; antigen presenting cells, APCs; graft-versus-host disease, GvHD; T-helper, Th; indoleamine 2,3-dioxygenase, IDO; tumor necrosis factor α, TNFα; granulocyte-macrophage colony-stimulating factor, GM-CSF; intercellular adhesion molecule 1, ICAM-1.

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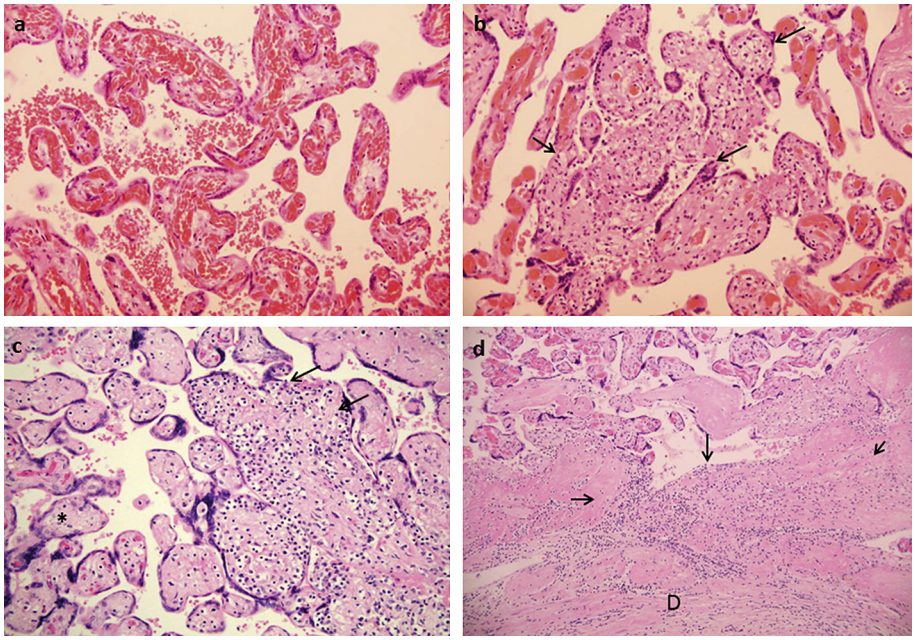

Fig. 1. a) Normal well vascularized terminal villi. b) Focal villitis – A group of villi showing chronic inflammation (arrows) surrounded by normal villi. c) Chronic villitis with avascular villi – the villi on the right show active chronic inflammation (arrows), whilst on the left the villi show burnt-out villitis with hyaline fibrosis (*), loss of fetal vessels and minimal residual inflammation. d) Basal villitis – this group of villi at the placental base, adjacent to the decidua (D), show chronic inflammation (arrows). All are hematoxylin and eosin (H&E) stained. a, b, c x40 and d x25 objective.

both proximal and distal stem villi (and sometimes chorionic plate) involvement is present [2]. As recently summarized [8], the major inflammatory patterns identified in VUE include lymphohistiocytic, lymphocytic, lymphoplasmocytic lesions, and granulomatous inflammation with multinucleate giant cells [5,7,9]. Albeit a wide spectrum of pathological features has been outlined, no definite histological diagnostic criteria for VUE currently exist [7,9]. Inflammation of the stem villous and/or chorionic vessels may result in luminal obliteration and/or thrombosis, causing peri- and true-vasculitis. Any resultant luminal thrombosis/obliteration and subsequent loss of villous blood supply are termed 'obliterative fetal vasculopathy' which is associated with more severe and significant pregnancy complications [2].

VUE severity is graded according to total villi involvement, and reflects the extent of the placental inflammatory process [2,7]. Even the most severely affected placentae show only up to 10% villi involvement [2]. Redline R, et al. [2] define "low grade lesions" as less than 10 villi (per focus) involvement which may be focal or multifocal. High grade lesions involve more than 10 villi (per focus) and are either patchy or diffuse. Similar but different grading systems have been utilized by other groups [7,9], again indicating the heterogeneity inherent to VUE's classification.

The cellular composition and origin of the inflammatory infiltrate in VUE is predominated by T lymphocytes (42% (33–66% range)) and macrophages (54% (33–66% range)) [3,10]. B-lymphocytes are also present, but in smaller numbers comparatively (2%) [10]. Using conjoint immunohistochemistry and in-situ hybridization (IHC-ISH), significant numbers of intervillous maternal CD3+ lymphocytes (T cells) and CD68 + macrophages of both maternal and fetal origin (differentiated using a Y-specific chromosome probe) have been demonstrated [11,3]. Contradictory to earlier findings [12], both CD8+ and CD4+ T cell populations are reportedly present, with CD8+ subtypes outnumbering CD4+ T cells in all villitis cases (CD4+:CD8+ ratio ranged from 0.02 to 0.87 (median = 0.31)); the exact nature of theses CD8+ T cells remains unknown [10,3]. Importantly, in 2011 the relative numbers of T regulatory cells (CD4+ CD25+ FoxP3+) (TReg cells) were also found to be increased in villitis lesions compared to control non-inflamed placentas [13].

The incidence of VUE in term placentae is considered to be 10% [14]. However, the lack of uniformity in the histological diagnostic criteria and tissue sampling methods and populations investigated has resulted in a wide spectrum of reported diagnostic rates, 2%–33.8% [8,14].

The challenges of consistent histological diagnosis have been well described. This includes significant observer error rates even amongst a group of experienced pathologists; intra- and inter-observer agreement of 84.7% and 81% respectively [6]. The main issues identified include subjective histologic criteria and variable diagnostic thresholds. Attempts to re-define VUE using immunohistochemistry for major histocompatibility complex (MHC) class II antigens have failed since the markers are not exclusive to VUE. Furthermore, some VUE placentas did not demonstrate MHC II immune-reactivity [15]. Considering the optimal number of placental blocks examined, VUE detection peaks at 4 sections, and 90% of lesions may be accurately identified using a standard 2–3 block sampling technique [2,7,8,16].

3. Clinical implications of VUE

Normal pregnancy remains the most common outcome in association with VUE both at term and preterm [17,18]. However, there is evidence to suggest VUE is not simply a "benign placental lesion". VUE has been associated with a range of adverse pregnancy outcomes as summarized in Table 1; pre-term labor (PTL) [19–21], intra-uterine growth restriction (IUGR) and small for gestational age (SGA) [5,7,9,17,18,20,22–27], spontaneous pregnancy loss [7,20,28,29], cerebral palsy (CP) and long-term neurological impairment (NI) [30], stillbirth [7] and perinatal mortality [9,28].

Adverse clinical pregnancy outcome corresponds with histologically defined VUE severity [7,9]; therefore more diffuse villitis is associated with poorer clinical outcomes [30]. This has also been