Classification of Villous Maldevelopment

The histopathology of villous maldevelopment is based on the light microscopy of paraffin sections. Thus, the normal and pathological features of the placenta are usually described in terms of the two dimensions apparent by light microscopy. These two-dimensional findings very often do not reflect the underlying three-dimensional malformation of villi, as becomes particularly obvious when considering the pathologically meaningful finding of “syncytial knotting” (Tenney-Parker changes).

Syncytial Knotting

SYNCYTIAL KNOTTING: ARTIFACT OR MEANINGFUL PATHOLOGICAL FINDING

In past decades several studies have revealed that the two-dimensional impression does not always reflect the three-dimensional structure. Küstermann (1981) used reconstructions of serial paraffin sections to show that most sprouts and bridges are in fact flat sections of irregularly shaped villous surfaces. Burton (1986a,b, 1987), who worked with plastic serial sections, and by Cantle et al. (1987) and Kaufmann et al. (1987), who compared light microscopic findings of villous sections with scanning electron microscopy of the identical material (Figure 15.1), arrived at similar conclusions. All three groups concluded that most of the syncytial knots, syncytial sprouts, and syncytial bridges, summarized as syncytial knotting or Tenney-Parker changes (for definition, see Chapter 6) proved to be only tangential sections of the villous surface. The true interpretation is of considerable importance for aspects of placental pathology, as the histological appearance of syncytial knotting is widely accepted as a diagnostic indicator of placental ischemia, for example, in preeclampsia (Tenney & Parker, 1940; Alvarez et al., 1964, 1969, 1970; Schuhmann & Geier, 1972).

Küstermann’s (1981) statement that all sprouts, knots, and bridges of the mature placenta must be interpreted as sectional artifacts brought about the question whether the histopathological experience should be abandoned. Küstermann’s results were largely corroborated by the studies of Burton (1986a) and Cantle et al. (1987). At the same time, it became apparent (Kaufmann et al., 1987) that despite this new interpretation the diagnostic value of “syncytial knotting,” even though in most cases representing artifacts, was still useful. As is described next, they are significant artifacts that point to a characteristic deformation of the terminal villi. This deformation is usually caused by abnormal villous angiogenesis resulting from abnormal placental oxygenation (see Figure 15.6). Therefore, the final conclusions drawn by Alvarez et al. (1969, 1970) are generally correct: The diagnostic value of the two-dimensional findings of syncytial knotting remains.

INTERPRETATION OF SYNCYTIAL KNOTTING

Küstermann (1981) and Burton (1986a) used three-dimensional reconstructions of serial sections to verify that most knots, sprouts, and bridges are only flat sections (see Figure 15.4), a point that can be demonstrated even more impressively in two other ways. Cantle et al. (1987) prepared 10 μm epoxy resin sections stained with toluidine blue. This dye does not infiltrate the resin and stains it only superficially. The resulting light microscopic picture corresponds to that of a semithin section of 0.5 to 1.0 μm (see Figure 15.2A). When studying the same section with phase contrast microscopy, one obtains a view of the complete 10 μm section of the identical material. When comparing the two pictures of the same section shown in Figure 15.2B, one easily realizes that the “thick section” does not show any sprouts, whereas the “thick section” reveals three apparent sprouts that were obviously tangential sections of the trophoblastic surface.

This finding is in agreement with the experience of all electron microscopists who have studied the placenta: knots, sprouts, and bridges are common in paraffin sections (5–10 μm), rare in semithin sections (0.5–1.0 μm), and mostly absent in the ultrathin sections (0.05–0.1 μm) prepared for electron microscopy. The situation is schematically depicted in Figure 15.3.

Similar conclusions were deduced when we prepared semithin sections for light microscopy and subsequently removed the epoxy resin from the remaining tissue block. The remaining villi were studied with the scanning electron microscope and compared to the semithin section (see Figure 15.1) (Cantle et al., 1987). Using this method, real sprouts and bridges as well as flat-sectioned villous surfaces can easily be identified and compared to the sectional picture of this tissue. It became evident from such material that branching, twisting, and coiling of villi (e.g., as a result of hypoxia) enhances the chance of tangential sectioning of trophoblastic surfaces and thus increases the number of artificial “knots,” “sprouts,” and “bridges” (see Figure 15.6).

On the other hand, scanning electron microscopic proof was presented by Schiebler and Kaufmann (1981), Burton (1986b, 1987), and Cantle et al. (1987) that not all sprouts, knots, and bridges are sectional artifacts; rather, few real such trophoblastic specializations do exist. They may serve (1) as first steps of villous sprouting, that is, formation of new villi (trophoblastic or syncytial sprouts) (Boyd & Hamilton, 1970; Cantle et al., 1987; Castellucci et al., 1990); (2) as...
a mechanism of extrusion of old syncytial nuclei (Martin & Spicer, 1973; Jones & Fox, 1977), most of the latter meanwhile identified as being apoptotic in nature (Huppertz et al., 1998); or (3) as simple mechanical aids to establish junctions between neighboring villi (syncytial bridges) (Cantle et al., 1987).

Cantle et al. (1987) suggested the following criteria for discriminating between true trophoblastic specializations and tangential sections (Figure 15.5).

- **True syncytial sprouting** resulting from trophoblastic proliferation is usually characterized by smooth surfaces with well-developed microvilli and loosely scattered, ovoid nuclei (see Figures 6.11A,B). Only incidentally do they fuse with neighboring villi to form syncytial bridges (see Figures 6.12A,B; 15.1A).
- **Degenerative, apoptotic knotting** results in knot- or sprout-like structures showing smooth surfaces, mostly devoid of microvilli; the densely packed nuclei show highly condensed chromatin, the most peripheral nuclei usually displaying annular chromatin condensation (see Figures 6.10A, 6.18, 6.22).
- **Flat sections (syncytial knotting, Tenney–Parker changes)** result in knots, sprouts, and bridges that are irregularly shaped and notched (see Figures 6.10C; 15.1A); they are characterized by heterogeneous nuclear shapes as these are typical for syncytiotrophoblast. The apparent numerical density of nuclei increases with section thickness.

Not only the structural features but also the stage of pregnancy and the type of villi involved, may be helpful for discrimination between the true sprouting, apoptotic shedding, and trophoblastic flat sectioning (Figure 15.5).

Generally, in paraffin sections of the **young placenta** most sprouts attached to immature intermediate and mesenchymal villi are signs of villous sprouting; less often are they sites of extrusion of apoptotic nuclei. Only a minority is artificially produced by trophoblastic flat sectioning. In contrast, in paraffin sections of the **mature placenta**, most knots, sprouts, and bridges are caused by flat sectioning; this is particularly true for those found in conglomerates of terminal villi. Far fewer are sites of accumulation of apoptotic nuclei. Only a very small minority, mostly arising from immature intermediate villi located in the centers of the villous trees, represents real villous sprouting.

**ARTIFICIAL KNOTTING AS RELATED TO VILLOUS SHAPES IN PARAFFIN SECTIONS**

The question of how to interpret knots, sprouts, and bridges relates to the more relevant question of how to interpret villous shapes