Histology of the Persistent Ductus Arteriosus in Cases of Congenital Rubella

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SUMMARY Histologic study of the persistent ductus arteriosus in case of a congenital rubella syndrome revealed that this persistency is probably due to an arrest in the development of the ductus. Histologically, it resembles a very immature ductus and not the most common type of persistent ductus arteriosus. The earlier finding, that in the human ductus arteriosus, the presence of an extensive subendothelial elastic lamina is incompatible with anatomic sealing, still holds.

THE RELATION between maternal rubella and congenital malformations in infants exposed to the infection in utero was first observed by Gregg. Since then many abnormalities have been shown to be related to maternal rubella.

Congenital heart disease is seen in about two-thirds of the infants with congenital rubella, and persistent ductus arteriosus accounts for about one-third of the anomalies. Persistent ductus arteriosus may occur alone or with other heart defects.

In the present study we describe the histology of two cases of persistent ductus arteriosus as part of the rubella syndrome and discuss whether these ducts differ from the persistent ductus arteriosus seen without a previous rubella infection.

Case Reports

Persistent ductus arteriosus material was obtained during surgery in two female children with a congenital rubella syndrome.

The first child (case 1) was 6 years old at the time of surgery. She was born at 37 weeks of gestation and weighed 1570 g at birth. In addition to a persistent ductus arteriosus the following rubella stigmata were seen: bilateral deafness, bilateral cataract, microcephaly, micro-ophthalmy, peripheral pulmonary stenosis, mental retardation and growth retardation. Rubella-specific IgM antibody was demonstrated with immunofluorescence and a culture for rubella virus was positive at age 9 months.

The second child (case 2), age 2 years, also had the typical stigmata of the rubella syndrome: bilateral deafness, pectus carinatum, mild peripheral pulmonary stenosis and growth retardation. The infant, born at 37 weeks gestation by cesarian section, had a birth weight of 2000 g. The mother suffered an attack of clinical rubella with lymphadenopathy and a typical rash after contact with a daughter who had the infection. Postnatal confirmation of a rubella infection in the infant has been established by a hemagglutinin inhibition test.

In the first child only part of the ductal circumference was obtained for study. In the second a complete ring of ductal tissue was removed during operation. The ductal tissue was fixed and serially sectioned after routine histologic procedures. Hema-toxylin-eosin, azan, and Van Gieson elastic tissue stains were used. The histology of these ducts was compared with that of persistent ducts without a rubella history, to normal ducts in term infants and to the different stages of histologic maturation seen during gestation.

Results

The wall structure is very similar in both rubella ducts (figs. 1 and 2). The absence of intimal thickenings or cushion formation is remarkable. Subendotheliahy an elastic lamina is distinguishable but is not equally clear at all sites. This is the only elastic lamina present, which is therefore considered to be the internal elastic lamina. It is an important landmark while studying the histology of the normal ductus arteriosus, marking the borderline of intima and media (fig. 3).

In the persistent rubella ducts we studied, the internal elastic lamina is situated underneath a thin intima, which consists of endothelium and a very thin subendothelial layer. The media contains fine elastic fibers, also seen in normal ducts. Smooth muscle cells are present, but the amount seems to be reduced. More collagen is seen in the media. At some places the inner third of the media can be distinguished from the outer two-thirds by a more longitudinal orientation of the muscle fibers (fig. 4). The characteristics of a ductus with normal anatomic closure, i.e. mucoid lakes, cytolytic necrosis and postnatal intimal proliferation, are absent.

The histology of the persistent rubella ductus resembles that seen in an immature ductus early in gestation, when intimal cushion formation has not yet started.

The histologic stages of normal ductal maturation and the histology of a persistent ductus with and without an obvious relation to maternal rubella are schematically visualized in figure 5.

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Discussion

Permanent or persistent patency of the ductus arteriosus is a clinically well known congenital heart malformation that usually requires surgical correction. If a ductus is still patent in a full-term infant after 3 months of life, spontaneous closure is not likely to occur. In preterm infants this period may be expanded to 1 year. A histologic study in infants of various ages revealed that a ductus that is still patent after 3 months of age shows a characteristic histology. In these cases there is always a subendothelial elastic lamina, which should be considered either the internal elastic lamina or an additional lamina. Also, in patients younger than 3 months, this abnormality was encountered occasionally. A more recent study on the histologic maturation of the ductus during gestation confirmed our initial hypothesis that the histologic abnormality, underlying permanent patency, is primary; it does not develop after birth as a result of the prolonged patency.

The most common type of persistent ductus in the human is that with two elastic lamina: the normal internal elastic lamina, situated between intima and media and an additional subendothelial elastic lamina on top of the cushions. Cases with elastification of the ductal wall, so-called aortification, are more rare, as are intermediate types.

The study of the development of the ductus arteriosus during gestation also supports the view that the presence of an extensive subendothelial elastic lamina is incompatible with definitive anatomic sealing, although clinically temporary functional closure could be achieved with indomethacin. The histologic structure of the persistent ductus in the congenital rubella syndrome most resembles that of an immature ductus without intimal cushion formation and, consequently, with a subendothelial elastic lamina bordering the lumen. It is not surprising, therefore, that it remains patent, and we may assume that treatment with indomethacin would not have resulted in definitive anatomic sealing.

Reports of the histology of the ductus arteriosus in cases of congenital rubella are scarce. However, the available data concur in that the muscular wall is thin, no intimal thickening is seen and the internal elastic lamina may be ill-defined. This is consistent with our histologic findings.

Fibrous intimal proliferation is frequently reported as a pathologic finding in arteries in case of congenital
rubella.\textsuperscript{4}–\textsuperscript{15} Also in the two patients described in the present paper, peripheral pulmonary stenosis, most probably due to this process, was present. This intimal proliferation does not seem to occur in the ductus.

With regard to the pathogenesis of persistent ductus arteriosus in the congenital rubella syndrome, some relevant data are available. The rubella virus is considered not to be a teratogenic agent in the usual sense of dysmorphogenic development; rather, it causes a mitotic arrest resulting in differential retardation of

**Figure 3.** Transverse section of the ductus arteriosus of a 12-day-old infant. The ductal wall shows all features typical for normal anatomical closure. ic = intimal cushion; iel = internal elastic lamina; m = media; ml = mucoid lake; pip = postnatal intimal proliferation. Van Gieson elastic tissue stain; magnification × 20.

**Figure 4.** Detail of the ductal wall of case 2, showing that the fibers of the inner part of the media (m) are more longitudinally orientated than those of the outer part. Hematoxylin-eosin stain; magnification × 90.

**Figure 5.** Schematic representation of various forms of ductus arteriosus. ic = intimal cushion; iel = internal elastic lamina; cn = cytolytic necrosis; m = media; ml = mucoid lake; mi = medial indentation; pip = postnatal intima proliferation; sel = subendothelial elastic lamina. Maturation stages normal ductus arteriosus: I = immature stage; II = intermediate stage; III = mature stage. Types of persistent ductus arteriosus: IIIa = most common type, with intimal cushions and internal elastic lamina. On top of the cushion lies the additional subendothelial elastic lamina. IIIb = more rare type, with aortification of the ductal wall. IIIc = type of persistent ductus seen in case of congenital rubella. This type resembles stage I.
tissue growth. This theory can very well be applied to the ductus arteriosus in the rubella syndrome. The vessel does not show a grossly abnormal wall structure. It most resembles an immature ductus, normally seen during the second and third trimester of pregnancy, thus illustrating a developmental arrest.

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