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OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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Pediatrics 1963;32;895

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FETAL INFECTION IN CHICKENPOX AND ALASTRIM, WITH HISTOPATHOLOGIC STUDY OF THE PLACENTA

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THE SUSCEPTIBILITY of embryonic and fetal tissues to viruses is well known, and there are innumerable observations of congenital virus diseases manifested during intra-uterine life, at the time of birth or on the first days of the neonatal period.

Chickenpox, as a disease conferring a permanent immunity, is seldom seen in the neonatal period, since most pregnant women have acquired immunity and transfer it passively to the fetus. According to a recent review, only 17 cases have been recorded¹ in which cutaneous lesions of chickenpox appeared before the tenth day of life, with a mortality of 20%.

In the Quarterly Cumulative Index Medicus (1927 to 1959) only one report was found of so-called alastrim^{*} in the fetus or newborn.² However, numerous cases have been recorded³⁻¹⁴ of intra-uterine smallpox infection and of complications from smallpox vaccination during pregnancy.

Because of their rarity, four cases of congenital virus disease, two of chickenpox, and two of alastrim, with heavy cutaneous and visceral lesions, accompanied by unusual and extensive placental lesions, are herein reported.

MATERIAL

The present observations concern three children (Cases 1, 3, & 4) born at the Maternidade Carmela Dutra, in Rio de Janeiro, and one (Case 2) born at the Maternidade Clara Basbaum included through the courtesy of Dr. Grelle). Case 1 was that of a 2-day-old premature infant who presented

* Dorland's Medical Dictionary defines alastrim as a "specific contagious eruptive fever, resembling smallpox, being probably a mitigated form of that disease."

cutaneous lesions at the time of birth and whose mother had chickenpox approximately one month before delivery. Case 2 was that of a macerated abortion in which the mother had chickenpox during the fourth month of pregnancy. In Cases 3 and 4, both macerated abortions, the mothers had alastrim during the fifth and fourth months of pregnancy.

Unfortunately the diagnoses were made retrospectively, so it was impossible to trace the whole history of maternal infection with chickenpox or alastrim during pregnancy. Our information was limited to the history as reported to the obstetricians. We did not make an epidemiologic survey or perform viral studies concerning these cases; however, in three of them we found fetal lesions and inclusions in the decidual cells compatible with the clinical diagnosis. In Case 2, in which the mother had had chickenpox, only nuclear lesions were detected, which, in fact, could have been misdiagnosed only as herpes simplex. In Case 3 and 4 characteristic protoplasmic inclusions of smallpox or alastrim were found. In Case 1 no cell inclusions were observed, but it is recognized that absence of inclusions does not preclude the presence of viral infection.

The fetal and placental tissues were fixed in 10% formalin and embedded in paraffin; the stain routinely used was hematoxylin-eosin.

CASE REPORTS

Case 1

HISTORY: The mother was a 24-year-old white primipara. Her last menstrual period occurred in February, 1953; the probable date of delivery was in November. The result of a Wassermann test was negative. She had mumps during the first days of pregnancy. In September (the seventh

(Submitted for publication, November 6, 1961; accepted April 15, 1963.)

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PEDIATRICS, November 1963



FIG. 1. Case 1. Areas of necrosis in the kidney.

month) she had high fever for 3 days, accompanied by cutaneous lesions diagnosed as chickenpox by a physician. The delivery was normal one month afterward (October). The mother presented cicatricial cutaneous lesions during the puerperium. The premature female infant weighed 1,700 gm, and the length was 48.5 cm. Lesions of "impetigo" were spread over all the cutaneous surface and scalp. The infant did not pass meconium or urine and could not be fed because of reflux of the food through the nose. She died 2 days after birth.

AUTOPSY FINDINGS: Autopsy revealed a normal premature infant with deep, ovoid, and well-limited cutaneous ulcerations covered by creamy-yellow material or by crusts localized on the scalp, face, trunk, and limbs.

In the head, vessels of the leptomeninges were excessively tortuous and congested. Whitish-yellow calcareous areas, irregularly spread on the nervous tissue, were most numerous on the cerebral and cerebellar cortices and invaded the leptomeninges. These were strongly suggestive of lesions produced by *Toxoplasma*.

In the thoraco-abdominal cavity, the lungs adhered to the costal framework and the diaphragm. Foul-smelling, purulent liquid was seen in the abdominal cavity, with streaks of fibrin adherent to the viscera and to the parietal layer of peritoneum. Intestinal loops were adherent and partially covered by the omentum. Well-limited sinuous whitish areas, isolated or confluent, were irregularly spread on the thymus, heart, lungs, liver, pancreas, kidneys, and adrenals. (Fig. 1). Deep and well-limited ulcers, some of them perforated, were present in the intestines and stomach.

Microscopic examination of the skin revealed

slight edema of epithelial cells, with margination of the chromatin. Ulcerated areas were accompanied by necrosis of the dermis and sometimes of the subcutaneous tissue, with chronic cellular infiltration in the dermis. In many organs, large irregular areas of necrosis, sharply demarcated from the normal parenchyma with discrete or absent peripheral inflammatory reaction, exhibited deposits of calcium salts in their central portions; in these partially necrotic areas, all the structures had disappeared and few vessels were seen. Identical foci of necrosis were observed in the lungs, liver, kidneys, adrenals, thymus, pancreas, myocardium, and intestines (Fig. 2). Necrotic areas in the brain were numerous; the grossly involved cortical, subependymal, and basilar structures of the cerebrum were the sites of tissue destruction, in which all elements had undergone dissolution, leaving tissue debris, showing extensive calcification; the lesions were sharply demarcated. Results of the search for *Toxoplasma* were negative.

Case 2

HISTORY: The mother had chickenpox in fourth month of pregnancy and almost one month afterward gave birth to a macerated female fetus, weighing 520 gm, with a length of 25 cm.

AUTOPSY FINDINGS: The macerated fetus was without external anomalies, with cutaneous lesions in the shape of small, irregularly spread, whitish spots, most abundant on the legs and abdomen. The visceral alterations were only those of maceration.

Microscopy revealed foci of necrosis in lungs, liver, spleen, adrenals, and kidneys. The placenta was round, 12 cm in diameter, and weighed 280 gm. The cotyledons were not well limited and were whitish in color, with small firm areas comparable to "rice seed." The fetal surface was normal; the adnexa showed signs of maceration; the cord was 23 cm in length and twisted.

The villi showed signs of immaturity and were partially surrounded by heavy exudate, consisting of necrotic material, leukocytes, and nuclear fragments, which filled the intervillous space (Fig. 3). Most of the villi were partially or entirely degenerated; the epithelium had disappeared in areas in contact with the aforementioned material. Some villi presented granulomatous lesions in the stroma, whose center was occupied by a small area of necrosis surrounded by epithelioid cells, by a few giant cells of foreign body type, and by round cells. Intercellular deposits of fibrinoid material and infiltration of leukocytes were seen in the decidua. Some decidual cells presented intranuclear inclusions, such as an eosinophilic central homogeneous mass surrounded by a clear halo, separating it from the nuclear membrane, pushing the chromatin to the periphery of the nucleus (Fig. 4).

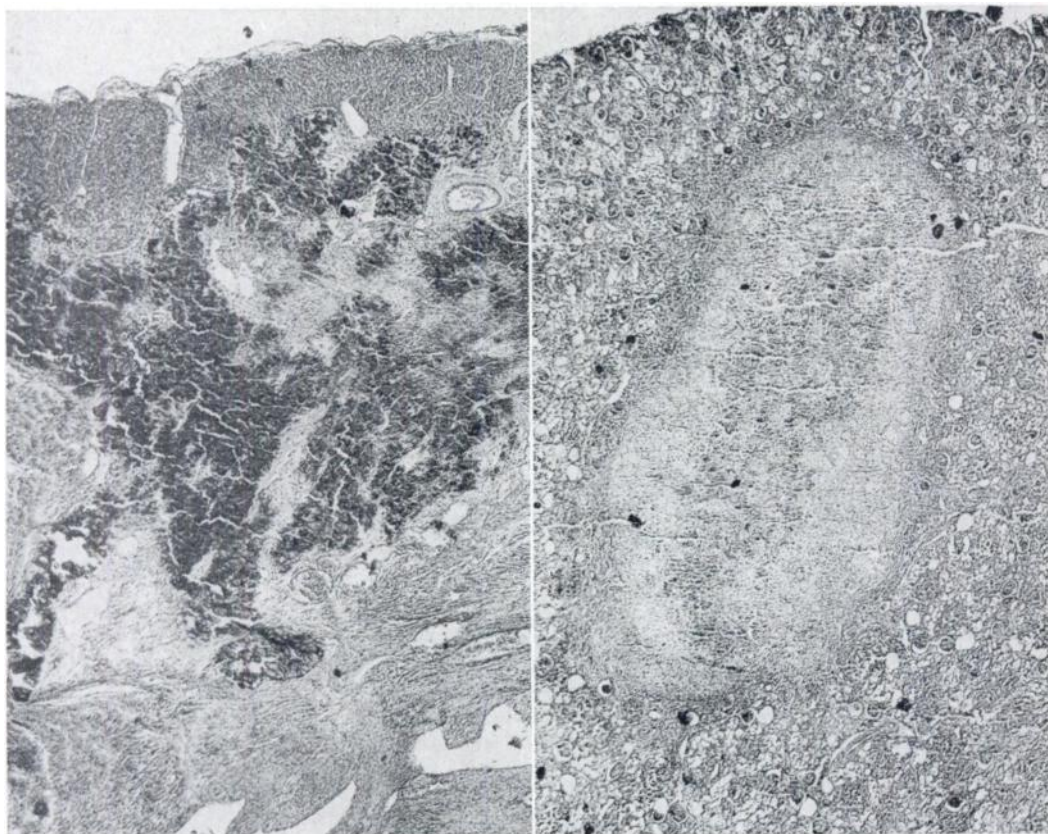


FIG. 2. Case 1. Extensive well-circumscribed areas of necrosis in the myocardium and kidney, with calcium salt deposits. ($\times 37$)

Case 3

HISTORY: The mother was 23 years old, white, para 1, gravida 2, and Wassermann negative. The first pregnancy was normal, the child was alive and well. For the second pregnancy the last menstrual period occurred in July, 1955; the probable date of delivery was given as May, 1956. In December, 1955 (fifth month), the mother had alastrim, at which time fetal movements ceased. Delivery was normal 2 months later. The fetus was macerated, female, and weighed 450 gm, with a length of 23 cm.

AUTOPSY FINDINGS: The macerated fetus was without external malformations. Whitish, well-circumscribed, round cutaneous lesions (3-5 mm), slightly prominent with depressed centers were over all the body, including the scalp (Fig. 5). The brain had lost its normal aspect, due to maceration. The liver was much enlarged, brownish-yellow, with a smooth surface, of normal consistency, and filled the greater part of the abdomen. The spleen was normal. The lungs adhered to the costal framework and presented whitish, round, superficial areas (2 mm), visible also on cut sec-

tion. The other organs showed only alterations produced by autolysis.

Microscopic examination was partially impaired by the degree of maceration of the viscera. Numerous foci of necrosis, without clear limits, with deposits of calcium salts in the center, were localized in the thymus, lungs, liver, kidneys, intestines, and adrenals. In the skin the cells of the superficial layer were covered with calcium salts in the nonnecrotic areas. Some perivascular round-cell infiltration appeared in the dermis. The placenta was round, 11 cm in diameter, and weighed 120 gm; the cord was laterally inserted. The cotyledons were pink, with many minute yellowish areas irregularly spread over the maternal and fetal surfaces, conferring a minute granular aspect; the cut surface revealed an identical aspect; the membranes were thick and dark.

A few normal appearing villi were in accord with the intra-uterine age. Numerous granulomatous lesions, tuberculoid in type, were noted in the villi or in the conjunctive strands (Fig. 6). These granulomas had central extensive necrosis, very like caseation. They were sharply circumscribed with wavy limits, surrounded by epithelioid

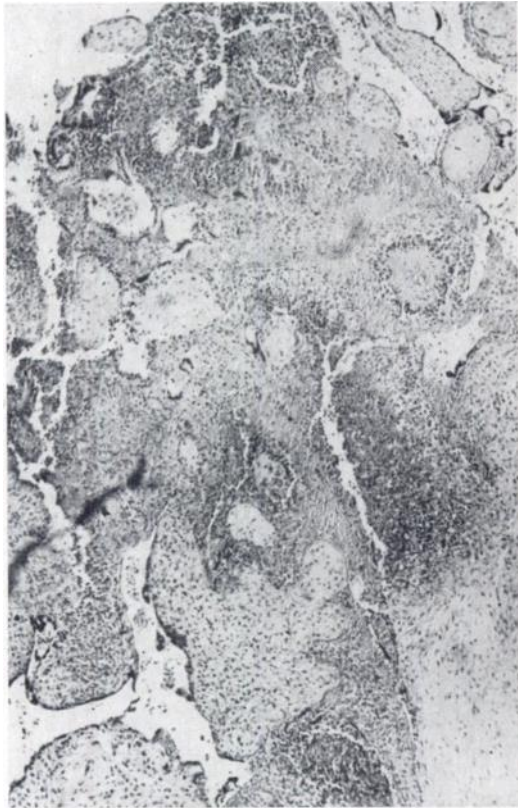


FIG. 3. Case 2. Section of the placenta showing partially or totally necrotic villi with granulomatous lesions in the stroma. Intervillous space is occupied by necrotic material. ($\times 34$)

cells, giant cells, histiocytes, and round cells. There were frequent groups of partially or totally impaired villi, bounded by deposits of fibrinoid, some with preserved syncytium and others with peripheral necrosis, giving the impression that the granulomatous lesions were located in the intervillous space. A few villi showed calcifications. In the decidua the fibrinoid deposit was abundant, and cell degeneration was remarkable. In these cells cytoplasmic acidophilic inclusion bodies of various sizes (Guarnieri bodies) limited by a clear space, were found (Fig. 7). Intranuclear inclusions were found equally; they were usually single, oval, and homogeneous masses, surrounded by a halo, separating them from the rest of the nucleus, which was sometimes reduced just to its nuclear membrane with a few chromatin dots. The nuclei and cytoplasmic inclusions were never found within the same cell.

Case 4

HISTORY: The mother was 27 years old, gravida 5 (three induced abortions, one cesarean, child

alive and well). Her last menstrual period occurred in July 19, 1956; the probable date of delivery was April 19, 1957. During the fourth month of pregnancy the mother had alastrim; 20 days later she had an abortion, delivering a macerated baby, male, weighing 180 gm, with a length of 20 cm.

AUTOPSY FINDINGS: The fetus was macerated with sloughing of the skin in large shreds. Small, whitish, round (5 mm), well-defined dorsal cutaneous lesions were irregularly spread. The viscera showed lesions caused only by maceration; slight hepatomegaly was noted.

Microscopic examination, in spite of the degree of maceration of the viscera, revealed minute and not well-defined areas of necrosis in the lungs, thymus, kidneys, spleen, adrenals and liver. The placenta was round, 11 cm in diameter, and weighed 90 gm; lateral insertion of the cord was noted. The maternal side appeared with a mottled aspect, with minute, intermingled pink and yellow areas. After fixation, innumerable small yellow dots of creamy consistency were seen in the parenchyma.

Microscopic examination, with low-power, showed a uniform aspect of the placenta. The intervillous space was occupied by a heavy exudate, consisting of amorphous material and leukocytes (polymorphonuclear cells and nuclear debris). The villi had a normal histologic appearance in accordance with the intrauterine age. An increase of round cells and little areas of necrosis appeared in the stroma. In the decidua, beyond the inflammatory exudate, was a deposit of fibrinoid material around the cells, many of which had degenerated. In the decidual cells there was cytoplasmic inclusion, such as a paranuclear homo-

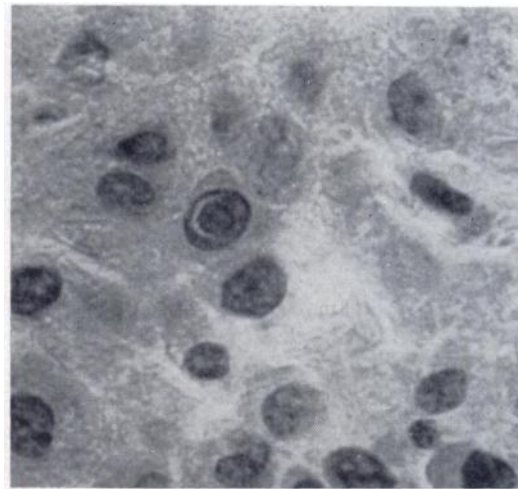


FIG. 4. Case 2. Presence of a nuclear inclusion in a decidual cell of the placenta. ($\times 1,000$)

genous corpuscle of irregular size, as described in Case 3. Inside the decidual cell nuclei some structures similar to inclusions were found; however, a badly fixed preparation impaired the interpretation of these findings.

COMMENT

Four cases of congenital virus diseases were observed (two of chickenpox and two of alastrim), in which maternal infection appeared in different stages of pregnancy, causing fetal abortions (Cases 2, 3, 4) and one premature delivery (Case 1) with death of the child 2 days after birth. In all cases identical visceral lesions were seen: focal areas of necrosis, with deposits of calcium salts in the central part, limited by discrete or absent inflammatory reaction and localized in almost all the viscera, including the nervous tissue.

The fetuses were in an advanced stage of maceration; this partially impaired the microscopic examination, although the foci of visceral necrosis could be easily visualized.

In Case 1 the child survived 2 days, and the mother presented cicatricial lesions of chickenpox at the time of delivery; the parenchymatous lesions were severe, localized mainly in the lungs, kidneys, pancreas, and brain. The encephalitic process was similar to that produced by congenital toxoplas-



FIG. 5. Case 3. Well-defined round and whitish areas with depressed central zones, localized on the skin and scalp.

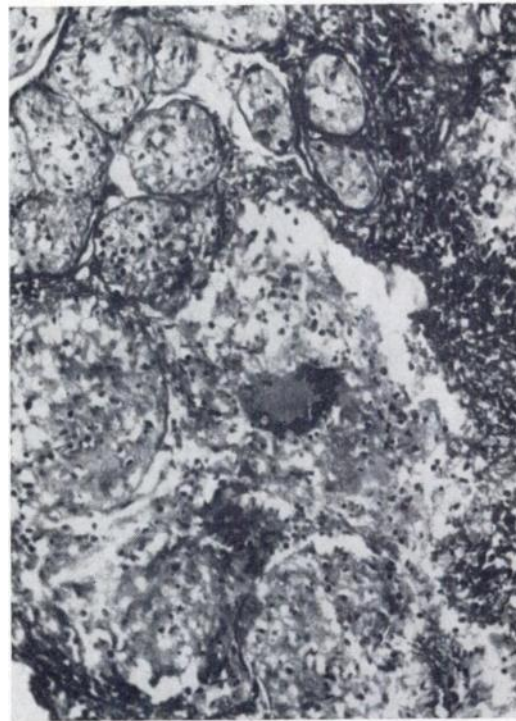


FIG. 6. Case 3. Group of partially or totally necrotic villi; a granulomatous lesion with a central typical giant cell. ($\times 405$)

mosis, but the toxoplasma organism was not found.

We would like to stress the fact that the fetal lesions presented the same characteristic pattern on gross and microscopic examination, both in the cases of chickenpox and alastrim. This type of lesion has been described in some virus diseases such as smallpox, vaccinia, herpes, and chickenpox.¹⁵⁻³³ The current literature emphasizes that the severity of the process is greatest during intra-uterine life or within the first days after birth.

The examination of the placentas (one case of chickenpox and two of alastrim) showed the presence of lesions that we had not had the opportunity to see described before (Quarterly Cumulative Index Medicus, 1927-1959). The gross examination showed tiny, yellow, creamy, irregularly scattered areas on the surface and in the interior of the placenta. Microscopy showed granulomatous lesions of tuberculoid type

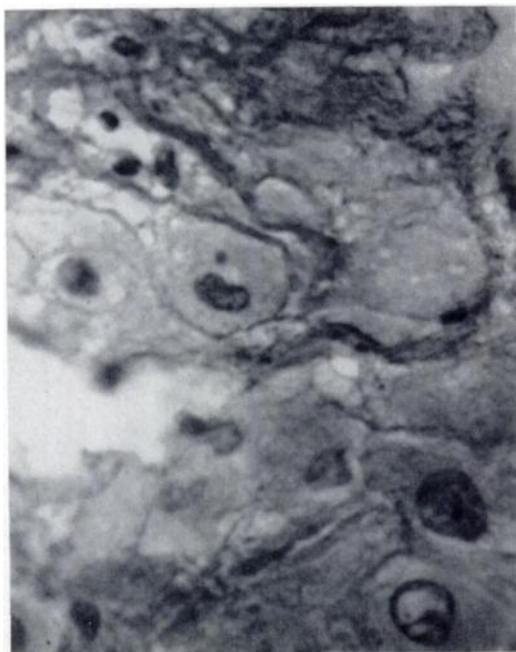


FIG. 7. Case 3. An inclusion body (Guarnieri body) in the cytoplasm of a decidual cell. ($\times 650$)

localized in the villi and the presence of necrotic material and cellular debris in the intervillous space, with partial or total destruction of the villous epithelium. The granulomas were easily identified in one case of alastrim (Case 3) and in one of chickenpox (Case 2); the microscopic appearance was the same in both. In Case 4 (alastrim), the necrotic process prevailed and the material that filled the intervillous space was particularly prominent. In the alastrim cases (Cases 3 & 4) there were seen protoplasmic inclusions in the decidual cells of the placenta as oval or irregularly shaped bodies (Guarnieri bodies), generally separated from the rest of the cytoplasm by a clear halo. The nuclear inclusions were characterized by an eosinophilic homogeneous central mass, also surrounded by a clear halo, often reducing the nucleus to a small fringe with a few dots of chromatin (Case 3). In Case 2 (chickenpox) only nuclear inclusions, with the aspect described above, were visualized. In the chorion and amnion there was marked infiltration by histiocytes and round cells.

The existence of fetal and placental lesions at the time of birth attest the congenital origin of the infectious process.

As Schick⁶ has insisted, new studies are necessary to determine which are the dangerous diseases for the fetus. Contact of pregnant women with patients with these infectious diseases, especially viral, must be prevented; the virus may invade the maternal circulation and reach the fetus, even in spite of maternal immunity, as has been proven in cases of chickenpox and German measles.³⁴

SUMMARY

Four cases of congenital viral disease are presented. Two cases were of chickenpox (a 2-day old infant and a macerated abortion) and two were of so-called alastrim, which is probably mitigated smallpox (macerated abortions). In all of them one special type of lesion was present: focal, irregularly sized areas of necrosis, with calcium deposits in the central part, sharply demarcated from the surrounding normal parenchyma and accompanied by slight or absent peripheral inflammatory reaction. In Case 1 (an infant who lived 2 days) such lesions were disseminated to all the viscera, especially the brain; the microscopic aspect was like that of congenital toxoplasmosis, and the microscopic examination revealed an essentially necrotizing inflammatory process with extensive calcification and glial reaction. The placenta, examined in two cases of alastrim and one of chickenpox, exhibited similar lesions both on gross and microscopic examination. On the surface and on the cut section there were numerous minute, irregularly spread yellowish areas. The histology showed the presence of tuberculoid-type granulomatous lesions in the villi and extensive areas of necrosis, the intervillous space being occupied by necrotic material and cellular debris. In one of the cases of alastrim (Case 3), there was predominance of the granulomatous lesions; in the other (Case 4), necrosis predominated; in Case 2, of chickenpox, beside the granulomatous lesions, there was extensive

necrosis. In the decidual cells there were characteristic inclusions of both the virus diseases. Such placental lesions apparently have not previously been described.

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