Placental involvement in congenital neuroblastoma

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SUMMARY We describe two cases of congenital neuroblastoma involving the placenta and review previously reported cases. The placentae in congenital neuroblastoma have a bulky, hydropic appearance, and contain tumour cells which are confined to the fetal circulation. The tumour emboli are not macroscopically identifiable. Pathophysiological mechanisms of placental involvement by fetal and maternal malignancies are considered. The rarity of this lesion may be artefactual, and may result from failure to examine grossly enlarged placentae in cases of stillbirth and hydrops fetalis. Congenital malignancy must be considered in the differential diagnosis of an abnormally large placenta.

Neuroblastoma is the commonest solid malignant tumour of childhood, arising from primitive neuroectodermal cells originating in the adrenal medulla or ganglia of the sympathetic nervous system. On rare occasions, it may present in the newborn period and these patients may have evidence of widespread metastatic disease. Congenital neuroblastoma associated with placental involvement is an even rarer occurrence and only six cases have been reported.1–5 We present two further cases of congenital neuroblastoma occurring in liveborn infants where there was extensive placental involvement.

Case reports

Case 1 (Hospital for Sick Children, Toronto)
This female infant was born by vaginal delivery at 40 wk gestation to a gravida 1, para 0 mother. The pregnancy was complicated by pre-eclampsia in the third trimester. The infant’s birth weight was 3800 g. She had mild respiratory distress and marked abdominal distention with dilated veins on the oedematous abdominal wall. The umbilicus was everted. The abdominal organs could not be palpated because of ascites. Radiography and ultrasonography showed gross hepatomegaly, but no evidence of calcification within the enlarged liver. There was a large mass in the left suprarenal region which extended across the midline and displaced the left kidney inferiorly. Liver scan demonstrated patchy uptake of radionuclide, suggestive of diffuse tumour infiltration. Haemoglobin was 12 g/dl; the urinary vanillylmandelic acid (VMA) excretion was increased to 226 μmol/24 h (448 mg) (normal < 5 μmol/24 h (0-1 mg)); the urinary homovanillic acid (HVA) was 200 μmol/mmol (322 mg/g) creatinine (normal < 22 μmol/mmol (1-2-35 mg/g)); and the carcinoembryonic antigen (CEA) was 4-5 μg/l (normal < 2 μg/l). The serum uric acid and serum aspartate aminotransferase concentrations were increased and the serum albumin was 2-5 g/dl. The baby was diagnosed as having congenital neuroblastoma of the left adrenal with hepatic metastases. She received a single course of total abdominal radiation (400 rads) and chemotherapy (vincristine and cyclophosphamide), but died on the 97th day of life. The mother’s 24 h-urinary VMA, total catecholamine and HVA were normal.

The placenta weighed 1150 g and its pale brown, bulky appearance was reminiscent of changes of erythroblastosis fetalis. Neuroblastoma cells were found within the fetal vascular channels of the chorionic villi, either singly or in clumps and rosettes (Fig. 1). At no point did the tumour cells extend through the vessel wall into the villous stroma, nor were they found in the intervillous space. Less than 5% of the villi contained tumour cells and scattered groups of villi were affected. The villi had an immature appearance, similar to that seen in materno-fetal rhesus incompatibility. The abundant stromal cells resulted in a hyperplastic appearance and cytotrophoblastic cells were prominent (Fig. 2). The individual neuroblastoma cells had dark, rounded nuclei with small amounts of poorly-demarcated cytoplasm. Electron microscopy demon-
strated membrane-bound secretory granules within the cytoplasm of the cells.

At necropsy the neuroblastoma was found to originate from the left adrenal and had spread to the right adrenal gland. Massive liver involvement was associated with gross ascites.

Case 2 (McMaster University Medical Centre, Hamilton)
This female infant was born to a gravida 1, para 0 mother at 38 wk gestation. The birth weight was 2770 g. The infant was hydropic with massive abdominal distention and extreme hepatomegaly. The other abdominal organs were obscured by ascitic fluid, and could not be palpated. The infant's haemoglobin was 10 g/dl and the serum albumin was 2.5 g/dl. She received an exchange transfusion with whole blood which resulted in transient improvement in her haemoglobin and albumin concentrations, but she remained anuric. Ultrasonograms revealed the presence of kidneys bilaterally. A bone marrow biopsy showed the presence of diffuse clusters of neuroblastoma cells within the marrow spaces. The placenta weighed 680 g and showed focally hydrotropic villi. Within the vessels of the villi numerous clusters of neuroblastoma cells were present. There was some stromal hypercellularity, but it was not as marked as in case 1.

The infant died aged 2½ days. Necropsy showed a massively enlarged left adrenal gland with complete replacement by neuroblastoma cells. Massive deposits of tumours were seen in the opposite adrenal gland, liver, kidney, bone marrow, spleen, myocardium, lung, pancreas, pancreatic lymph nodes, ovaries, dorsal root ganglia, celiac ganglion, small and large bowel, pituitary, thyroid, and middle ear.

Discussion
In addition to materno-fetal blood group incompatibilities, maternal disease (for example, diabetes mellitus, anaemia, cardiac disease), intrauterine infections, prolonged gestational periods and fetal anomalies (for example, anencephaly, trisomy 21 and other genetic disorders), congenital malignancies may cause placental enlargement. Six previous cases of congenital neuroblastoma are recorded.1–5 As in our present cases, the placentae had a hydrotic appearance with recorded weights of up to 1100 g. Two of the infants were stillborn and in the other four, the longest period of survival was 17 days. Fetal vascular channels within the placentae contained tumour deposits, but invasion of the stroma of chorionic villi was not found. There were no reports of spread into the maternal circulation.
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immature chorionic villi showing separation of fetal vascular channels from the trophoblast layer by abundant villous stroma. Haematoxylin and eosin x 800.

(intervillous space) nor evidence of metastases in the mother. As pointed out by Willis, tumour emboli that do not multiply and invade adjacent tissues are not metastases in the true sense of the word, and the previously reported cases of placental involvement in congenital neuroblastoma\(^1\) describe tumour embolism rather than the metastatic spread.

It is not clear why placental hydrops should develop in association with congenital neuroblastoma. Strauss and Driscoll (1964),\(^1\) when reporting the first cases, suggested an immune reaction to the tumour cells as the cause of the placental enlargement with increased numbers of Hofbauer cells and nuclear debris being present; however, an associated lymphocytic infiltrate was not described, nor was it a feature of our cases. Plugging of the placental vessels by tumour cells may be a factor, but placental enlargement may not necessarily reflect the extent of vascular involvement,\(^9\) and this mechanism can be invoked only if detailed morphometric studies assessing the extent of vascular deposits have been made. A case of congenital neuroblastoma with placental enlargement but without tumour emboli has been described.\(^7\) This would suggest that the placental changes are not merely the result of the presence of neuroblastoma cells. Increased placental growth may be a response to compensate for fetal anaemia,\(^5\) as the four liveborn infants and our present cases were anaemic. Obstruction of the placental venous return is another possibility, as has been postulated to occur in bilateral congenital nephroblastoma\(^8\) and congenital cystic adenomatoid malformations of the lung,\(^9\) both of which may present with placental enlargement. Placental enlargement may be found in diseases where changes in haemodynamics do not occur (for example, congenital syphilis and toxoplasmosis), and the pathogenesis of the placental changes seen in infants with congenital neuroblastoma remains uncertain. Both of our infants had evidence of massive liver involvement, and there was marked hypoalbuminaemia, and some of the placental hydropic change may have resulted from alterations in plasma proteins.

Other congenital lesions have involved the placenta. An enlarged placenta containing lymphoblastic cells was thought to have been due to a congenital leukaemia,\(^10\) although the stillborn fetus was not examined. A definite example of fetal leukaemic cells within chorionic villi was illustrated by Fox.\(^11\)

Two cases of placental involvement by congenital giant pigmented nevi have been reported.\(^12\)\(^13\) One
author "hypothesised" the filtration of nevus cells from the fetal circulation by the placenta. An alternate theory, based on the relative proximity of the developing umbilical stalk to the neural tube in the embryo, is that of aberrant migration of neural crest cells to the placenta. Interestingly, in both cases only the interstitial tissue of placental villi contained the pigmented nevus cells and they were not present within fetal vascular channels. When this is considered in the light of the apparent inability of congenital neuroblastoma cells to penetrate into the villous stroma in the placenta, abnormal migration rather than haematogenous spread becomes a more plausible hypothesis.

Though rare, placental metastases from a maternal neoplasm have been reported on more occasions than metastases from fetal neoplasms. Beside reports of leukaemia or lymphoma, at least 36 maternal neoplasms have involved the fetoplacental unit. Villous invasion has been documented in only a minority of the patients and the deposits of the maternal neoplasm have been located in the intervillous space in the majority of cases. In eight of the 18 instances of malignant melanoma, spread to the fetus occurred. As with fetal neoplasms, the inability of most maternal neoplasms to penetrate the chorionic villi is not understood. It may be due to the mechanical stability of the trophoblastic cell layer, or the possible control of tumour invasion by a fetal immunological mechanism. While the absence of lymphoid cells in the villi adjacent to the intervillous tumour deposits lends no morphological support to this latter hypothesis, the regression of metastatic malignant melanoma in two of the eight affected infants would suggest that the fetus does have some protective immunological mechanisms. In those instances in which invasion of chorionic villi by maternal tumour could not be demonstrated, but fetal involvement occurred, infarction of chorionic villi may have led to a breakdown of the placental barrier.

Just as the maternal immune system can destroy fetal erythrocytes which cross the placental barrier, it may have a similar protective function in the event of transplacental spread of congenital malignancies. Cells from a congenital neuroblastoma that gain access to the maternal circulation may, therefore, be sequestered and destroyed by the mother's immunological defences. It is likely that the patterns of placental involvement in cases of maternal and fetal neoplasms, reflect the complex, and poorly understood, immunological balance that exists in a normal pregnancy. Thus, as a general rule, maternal neoplasms are confined to the intervillous space, while fetal neoplasms are restricted to the chorionic villi. That this is an oversimplification is suggested by the relative rarity of choriocarcinomata invading the fetus, as opposed to metastatic spread in the mother; however, this exception does emphasise the importance of the trophoblastic layer in fetomaternal immunological balance.

In view of the important role of the placenta in the fetal circulation, it is uncertain whether the reported low incidence of placental involvement by congenital malignancies is real or artefactual. The placenta may not be available for examination in many infants, and when available, may not be examined histologically. The tumour emboli are not visible on gross inspection and are easily overlooked. The newborn infant may not manifest a congenital malignancy at the time of delivery and retrieval of the placenta may not be possible. The uneven distribution of tumour cells within placental villi may give rise to sampling errors; and the similarity to fetal leucocytes and nucleated erythrocytes allows misinterpretation. We emphasise the importance of placental examination, including detailed histological study, in all cases of hydrops fetalis or placental enlargement or both.

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