Chapter 11

Fetal tumors

(With the collaboration of Israel Goldstein)

INTRODUCTION

Fetal tumors are rare, but they have important implications for the health of both the fetus and the mother. The natural history and prognosis of most fetal tumors are well known. Once a fetal tumor has been detected, close surveillance by a multidisciplinary team of doctors is mandatory, with anticipation and early recognition of problems during pregnancy, labor and immediate postnatal life. When the sonographic diagnosis is uncertain, fetal tissue biopsy may be necessary to obtain a histological diagnosis. In rare cases, intrauterine treatment may be possible. Some fetal tumors may be malignant and could metastasize to other fetal organs and the placenta; maternal metastases in such cases are unknown. In contrast, on rare occasions, maternal malignancies (melanoma, leukemia and breast cancer) can metastasize to the placenta; in about half of the cases with placental metastases, mostly with malignant melanoma, the tumor can metastasize to fetal viscera.

Etiology and mechanisms of carcinogenesis

Developmental errors during embryonic and fetal maturation may result in embryonic tumors. One hypothesis is that more cells are produced than are required for the formation of an organ or tissue and the origins of embryonic tumors rest in developmental errors in these surplus embryonic rudiments. Embryonic tumors developing after infancy are explained by the persistence of cell rests or developmental vestiges. Developmentally anomalous tissue (such as hamartomas and dysgenic gonads) is a source of neoplasms in older children and adults. When any of this developmentally abnormal tissue is present at birth, it is inferred that the cells failed to mature, migrate or differentiate properly during intrauterine life.

Neoplastic transformation of cells in tissue culture and in vivo carcinogenesis are dynamic, multistep and complex processes that can be separated artificially into three phases: initiation, promotion and progression. These phases may be applied to the natural history of virtually all human tumors, including embryonic ones. Initiation is the result of exposure of cells or tissues to an appropriate dose of a carcinogen; an initiated cell is permanently damaged and has a malignant potential. The initiated cells can persist for months or years before becoming malignant. During the promotion phase, initiated cells clonally expand. Promotion may be modulated or reversed by a variety of environmental conditions. In the last phase, progression, the transformed cells develop into a tumor, ultimately with metastasis. Embryonic tumors can, therefore, be regarded as defects in the integrated control of cell differentiation and proliferation. A genetic model of carcinogenesis has also been introduced in an attempt to clarify the pathogenesis and behavioral peculiarities of certain embryonic tumors. According to this hypothesis, embryonal neoplasms arise as a result of two mutational events in the genome. The first mutation is prezygotic in familial cases and postzygotic in non-familial; the second mutation is always postzygotic.

Benignity of fetal and infantile neoplasms

Some neonatal and infantile tumors have a benign clinical behavior despite histological evidence of malignancy. Examples include congenital neuroblastomas and hepatoblastomas in the first year of life, and congenital and infantile fibromatosis, and sacrococcygeal teratomas in the first few months of life. The factors responsible for this 'oncogenic period of grace', which starts in utero and extends through the first few months of extrauterine life, are uncertain.

Association of neoplasia and congenital malformations

The concept that teratogenesis and oncogenesis have shared mechanisms is well documented by numerous examples. Probably, there is simultaneous or sequential cellular and tissue reaction to specific injurious agents. The degree of cytodifferentiation, the metabolic or immunological state of the embryo or fetus, and the length of time of exposure to the agent will determine whether the effect is teratogenic, oncogenic, both, or neither. Many biological,

chemical and physical agents known to be teratogenic to the fetus or embryo are carcinogenic postnatally. Alternatively, a teratogenic event during intrauterine life may predispose the fetus to an oncogenic event later in life. This would explain neoplastic transformation occurring in hamartomas, developmental vestiges, heterotopias and dysgenetic tissues. It is postulated that the anomalous tissues harbor latent oncogenes which, under certain environmental conditions, are activated, resulting in malignant transformation of a tumor.

Classification

A formal classification of fetal tumors does not exist. Apart from distinguishing solid from cystic lesions, probably the best classification should be by location. The main compartments of fetal tumors are the head and brain, face and neck, thorax (including the heart), abdomen and retroperitoneum, extremities, genitalia, sacrococcygeal region, and skin.

Prenatal diagnosis

The approach for prenatal diagnosis of fetal tumors should be based on three sets of ultrasound signs: general signs, organ-specific signs and tumor-specific signs. The general sonographic features, that should raise the suspicion of an underlying fetal tumor, include:

(1) Absence or disruption of contour, shape, location, sonographic texture or size, of a normal anatomic structure;

(2) Presence of an abnormal structure or abnormal biometry;

(3) Abnormality in fetal movement;

(4) Polyhydramnios; and

(5) Hydrops fetalis.

Polyhydramnios is particularly important, because almost 50% of fetal tumors are accompanied by this finding. The underlying mechanisms include interference with swallowing (such as thyroid goiter or myoblastoma), mechanical obstruction (such as gastrointestinal tumors), excessive production of amniotic fluid (such as sacrococcygeal teratoma), and decreased resorption by lung tissue in lung pathology. Intracranial tumors are also commonly associated with polyhydramnios and the mechanism may be neurogenic lack of swallowing or inappropriate polyuria.

Tumor-specific signs include pathological changes within the tumor mass (calcifications, liquefaction, organ edema, internal bleeding, neovascularization and rapid changes in size and texture). Organ-specific signs are rare, but in some cases they are highly suggestive of the condition (such as cardiomegaly with a huge solid or cystic mass occupying the entire heart, suggesting intrapericardial teratoma).

In some cases, normal and abnormal sonographic findings may mimic fetal tumors. Examples may vary from severe cases of bladder exstrophy (where the protruding bladder mass appears as a solid tumor-like structure), to rare cases of fetal scrotal inguinal hernia (where bowel loops occupy the scrotum, appearing as huge masses).

Prognosis

Apart from intracranial tumors (where the prognosis is generally poor), the prognosis for tumors in other locations is variable and depends on the size of the tumor (with resultant compression of adjacent organs), degree of vascularization (with the risk of causing heart failure and hydrops), and associated polyhydramnios (with the risk of preterm delivery).

INTRACRANIAL TUMORS

Intracranial tumors include teratomas, epidermoid, dermoid, germinoma, medulloblastoma, meningeal sarcoma, lipoma of the corpus callosum, oligodendroglioma, gangliocytoma, and glioblastoma, choroid plexus papilloma, tuberous sclerosis (Bourneville's disease), neurofibromatosis (Von Recklinghausen's disease), and systemic angiomatosis of the central nervous system and eye (Von Hippel–Lindau's disease).

Prevalence

Brain tumors are exceedingly rare in children, and only about 5% arise during fetal life; teratoma is the most frequently reported.

Etiology

Embryonic tumors are thought to derive from embryologically displaced cells. Brain tumors have been produced in animals by the use of chemical and viral teratogens. The relevance of these experiments to human brain neoplasms is unclear.

Diagnosis

A brain tumor should be suspected in the presence of mass-occupying lesions (cystic or solid areas), and a change in shape or size of the normal anatomic structures (such as shift in the mid-line). Cystic tumors and teratomas are usually characterized by complete loss of the normal intracranial architecture. In some cases, the lesion appears as a low echogenic structure, and it may be difficult to recognize. Hydrocephalus is frequently associated with brain tumors and may be the presenting sign. The ultrasound appearances of all intracranial tumors are similar and, therefore, precise histological diagnosis from a scan is almost impossible. Possible exceptions are lipomas (that have a typical hyperechogenic homogeneous appearance) and choroid plexus papillomas (that appear as an overgrowth of the choroid plexus). Identification of brain neoplasm associated with tuberous sclerosis, neurofibromatosis, and systemic angiomatosis of the central nervous system and eye can be attempted in patients at high risk; in most cases, however, antenatal sonography is negative, at least in the second trimester.
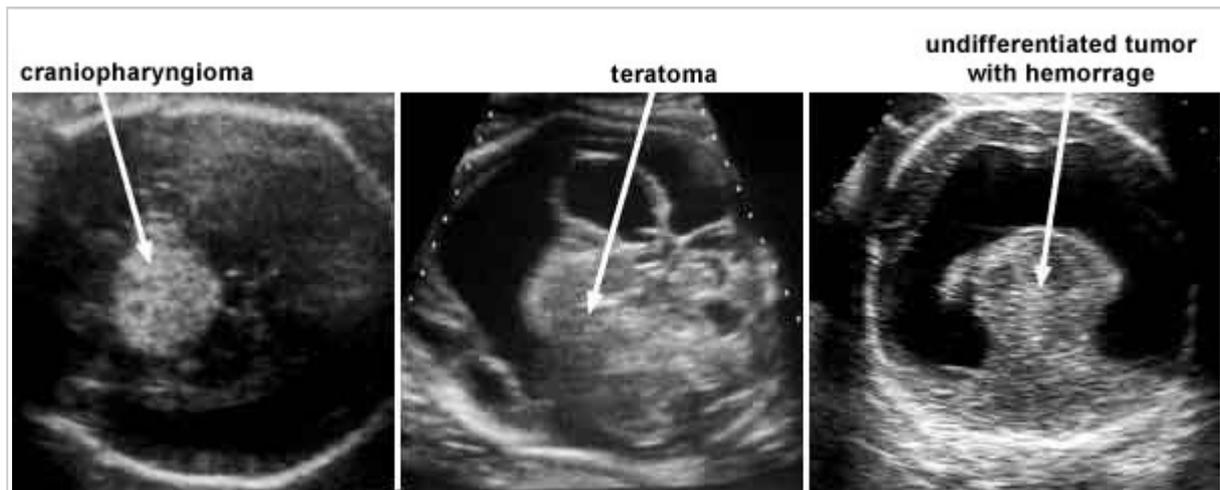

Prognosis

Prognosis depends on a number of factors, including the histological type and the size and location of the lesion. Congenital intracranial teratomas are usually fatal. The limited experience with the other neoplasms in prenatal diagnosis precludes the formulation of prognostic considerations.

TUMORS OF THE FACE AND NECK

Epignathus

This is a very rare teratoma arising from the oral cavity or pharynx. Most cases of epignathus arise from the sphenoid bone. Some arise from the hard and soft palate, the pharynx, the tongue and jaw. From their sites of origin, the tumors grow into the oral or nasal cavity or intracranially. The tumors, which are usually benign, consist of tissues derived from any of the three germinal layers; most of them contain adipose tissue, cartilage, bone, and nervous tissue. Prenatal diagnosis is suggested by the demonstration of a solid tumor arising from the oral cavity; calcifications and cystic components may also be present. Differential diagnosis includes neck teratomas, encephaloceles, and other tumors of the facial structures. Polyhydramnios (due to pharyngeal compression) is usually present. A careful examination of the brain is important because the tumor may grow intracranially. The outlook depends on the size of the lesion and the involvement of vital structures. Lesions detected antenatally have been very large. Polyhydramnios has been associated with poor prognosis. The major cause of neonatal death is asphyxia due to

airway obstruction. Surgical resection with a normal postoperative course is possible.
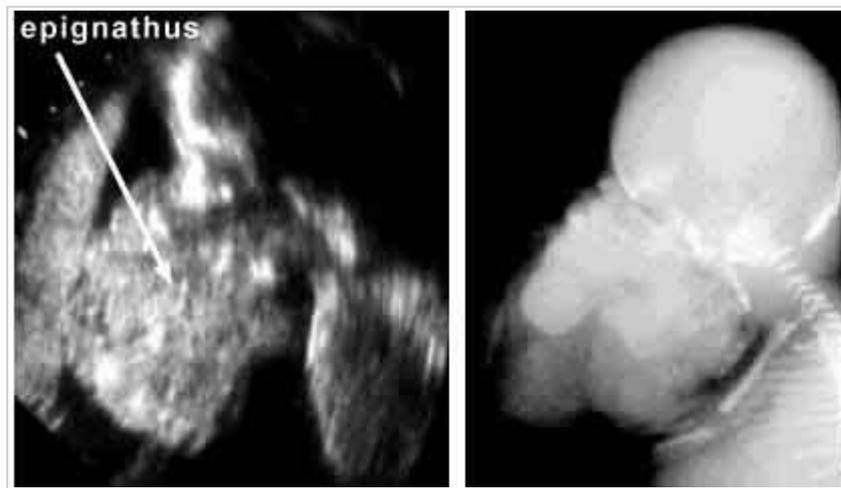
Myoblastoma

This is a very rare benign tumor, which usually arises from the oral cavity. The tumor occurs in females exclusively and it may be the consequence of excessive production of estrogens by the fetal ovaries under human chorionic gonadotropin stimulation. The ultrasound features are those of a large solid mass protruding from the fetal mouth. Vascular connections between the tumor and the floor of the oral cavity may be demonstrated using color Doppler ultrasound. Polyhydramnios (due to pharyngeal compression) is common.

Cervical teratoma

This is a rare tumor. Ultrasound features include a unilateral and well-demarcated partly solid and cystic, or multiloculated mass, calcifications (in about 50% of cases), and polyhydramnios (in about 30% of cases due to esophageal obstruction). The prognosis is very poor and the intrauterine or neonatal mortality rate (due to airway obstruction) is about 80%. Survival after surgery is more than 80% but, since these tumors tend to be large, extensive neck dissection and multiple additional procedures are necessary to achieve complete resection of the tumor with acceptable functional and cosmetic results.

Goiter

Fetal goiter (enlargement of the thyroid gland) can be associated with hyperthyroidism (the result of iodine excess or deficiency, intrauterine exposure to antithyroid drugs or congenital metabolic disorders of thyroid synthesis), hypothyroidism or an euthyroid state. Ultrasound diagnosis is based on the demonstration of a solid, anteriorly located symmetric mass, which may result in hyperextension of the fetal head. Polyhydramnios is common due to mechanical obstruction of the esophagus. The prognosis depends on the basic cause of the goiter. Most cases are in women with a history of thyroid disease. Fetal blood sampling can aid in determining fetal thyroid status, especially in women suffering from Grave's disease where a transplacental transfer of drugs or thyroid-stimulating antibodies may result in fetal goiter. Maternal therapy usually corrects fetal hyperthyroidism. Direct fetal therapy in cases of fetal hypothyroidism can be undertaken by amniocentesis or by cordocentesis and this can result in resolution of the fetal goiter.

TUMORS OF THE THORAX

Lung tumors

Fetal lung tumors have not been reported in the literature. Other lesions, which are malformations, and which may appear as solid masses in the thorax, include cystic adenoid malformation of lung and extralobar lung sequestration.

Mediastinal tumors

Mediastinal tumors (which include neuroblastoma and hemangioma) may cause mediastinal shift, lung hypoplasia, hydrops and polyhydramnios (due to esophageal compression).

Rhabdomyoma (hamartoma) of the heart

Rhabdomyoma (which represents excessive growth of cardiac muscle) is the most common primary cardiac tumor in the fetus, neonate, and young child; the birth prevalence is 1 per 10 000. In 50% of cases, the tumor is associated with tuberous sclerosis (autosomal dominant condition with a high degree of penetrance and variable expressivity). The ultrasound features are those of a single or multiple echogenic masses impinging upon the cardiac cavities. The prognosis depends on the number, size and location of the tumors. The clinical spectrum varies from completely asymptomatic to severely ill. The mortality rate in infants operated on within the first year of life is about 30%. Up to 80% of the infants with tuberous sclerosis have seizures and mental retardation, which are the most serious long-term complications of the disease.

Intrapericardial teratoma

In the majority of cases, the tumor is located in the right side of the heart. It may reach a size that is 2–3 times that of the normal heart. The tumor may be cystic or pedunculated. Pericardial effusion is always present and results from rupture of cystic areas within the tumor, or from obstruction of cardiac and pericardial lymphatic veins. Cardiac tamponade and hydrops may develop and the prognosis is very poor.

TUMORS OF THE ABDOMEN AND RETROPERITONEUM

Hepatic tumors

Primary hepatic tumors (hemangioma, mesenchymal hamartoma, hepatoblastoma and adenoma) are extremely rare. All hepatic tumors may show the same sonographic features: either a defined lesion (cystic or solid) is present or hepatomegaly exists. Calcifications may appear, and both oligohydramnios and polyhydramnios have been observed. The other tumors are very rare and little is known about their natural history. Hemangiomata are histologically benign and they regress spontaneously after infancy. However, occasionally, they are associated with arteriovenous shunting, congestive heart failure and hydrops, resulting in intrauterine or neonatal death.

Neuroblastoma

This is one of the most common tumors of infancy and is found in about 1 per 20 000 births. Neuroblastoma arises from undifferentiated neural tissue of the adrenal medulla or sympathetic ganglia in the abdomen, thorax, pelvis, or head and neck. Usually, the lesion is isolated, but occasional metastasis before birth may occur. Sonographically, the tumor appears as a cystic, solid, or complex mass in the region of the adrenal gland (directly above the level of the kidney and under the diaphragm). Occasionally, calcifications are present. Tumors arising from the sympathetic ganglia may appear in the neck, chest, or in the abdomen. There may be associated polyhydramnios and fetal hydrops. The tumor can metastasize in utero (placenta, liver, or blood vessels). The prognosis is excellent if the diagnosis is made in utero or in the first year of life (survival more than 90%), but, for those diagnosed after the first year, survival is less than 20%.

Renal tumors

Mesoblastic nephroma (renal hamartoma) is the most frequent renal tumor, while Wilms' tumor (nephroblastoma) is extremely rare. The sonographic picture in both tumors is of a solitary mass replacing the normal architecture of the kidney, and, in most cases, there is associated polyhydramnios. Cystic areas may appear in both tumors. Mesoblastic nephromas are benign, and nephrectomy is curative in the majority of cases. Wilms' tumor is a genetically heterogeneous group of malignant tumors and up to 60% of affected cases are associated with genetic syndromes (such as Beckwith–Wiedemann syndrome). Treatment of the tumor requires surgery, chemotherapy and sometimes radiotherapy.

TUMORS OF THE EXTREMITIES

Tumors of the extremities include:

(1) Vascular hamartosis; a malformation in which newly formed vessels proliferate;

(2) Hemangioma, a combined lesion of both skin and internal organs. The Klippel–Weber–Trenaunay syndrome should be considered in the differential diagnosis. The hemangiomas may vary in size and location. Some authors do not consider them to be true tumors, but rather suspect them to represent vascular malformations;

(3) Lymphangioma, a cavernous lymphangioma, which involves the lymphatic vessels and is related to cystic hygroma;

(4) Sarcoma (mainly rhabdomyosarcoma); this should be distinguished from infantile myofibromatosis.

TUMORS OF THE SKIN

Malignant melanoma is a rare tumor capable of metastasizing into other organs including the fetal liver, lungs and placenta.

SACROCOCCYGEAL TERATOMA

The sacrococcygeal region is the most frequent site of teratomas of the fetus.

Prevalence

Sacrococcygeal teratoma is found in about 1 per 40 000 births. Females are four times more likely to be affected than males, but malignant change is more common in males.

Etiology

This tumor is thought to arise from totipotential cells in Hensen's node. A theory of 'twinning accident' with incomplete separation during embryogenesis has also been proposed. The condition is sporadic but some cases are familial, with autosomal dominant inheritance.

Diagnosis

Sacrococcygeal teratomas usually appear solid or mixed solid and cystic (multiple cysts are irregular in shape and size). Occasionally, the tumor is completely cystic, and more rarely completely solid. Most teratomas are extremely vascular, which is easily shown using color Doppler ultrasound. The tumors may be entirely external, partially internal and partly external, or mainly internal. Polyhydramnios is frequent, and this may be due to direct transudation into the amniotic fluid and due to fetal polyuria, secondary to the hyperdynamic circulation, which is the consequence of arteriovenous shunting. Similarly, high-output heart failure leading to hepatomegaly, placentomegaly and hydrops fetalis can occur.

Sacrococcygeal teratomas

fluid   mixed   solid
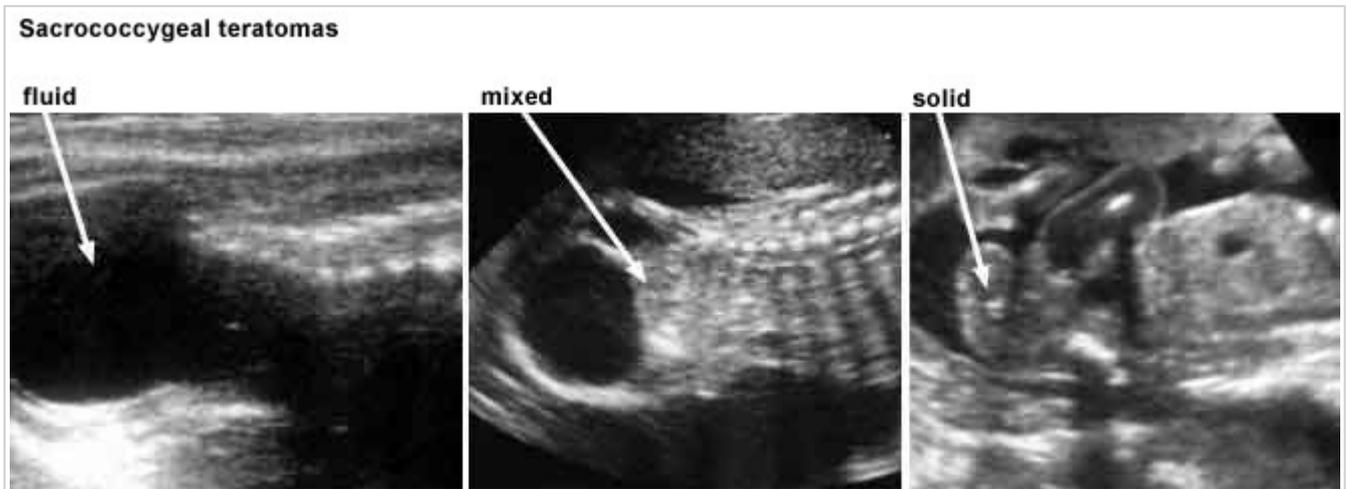
Prognosis

Sacrococcygeal teratoma is associated with a high perinatal mortality (about 50%), mainly due to the preterm delivery (the consequence of polyhydramnios) of a hydropic infant requiring major neonatal surgery. Difficult surgery, especially with tumors that extend into the pelvis and abdomen, can result in nerve injury and incontinence. The tumor is invariably benign in the neonatal period but delayed surgery or incomplete excision can result in malignant transformation (about 10% before 2 months of age to about 80% by 4 months).