Fetiform Teratoma (Homunculus)

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● ***Fetiform teratoma (homunculus)*** **is a term that has been given to a rare form of ovarian teratoma that resembles a malformed fetus. There are very few reported cases of this entity in the English language literature. In this report, we document a case of fetiform teratoma in a 23-year-old woman, gravida 0, who initially presented with a chief complaint of dyspareunia. The clinical and pathologic aspects of this rare entity are presented here, with a review of the English literature. Differentiating fetiform teratoma from the more highly developed fetus-in-fetu and ectopic pregnancy is also discussed.**

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The concept of a homunculus (Latin for ''little man,'' sometimes spelled ''homonculus'') is often used to illustrate the functioning of a system. In the scientific sense of an unknowable prime actor, it can be viewed as an entity or agent.

The term appears to have been first used by the alchemist Paracelsus. He once claimed that he had created a false human being that he referred to as the homunculus. The creature was to have stood no more than 12 inches tall and did the work usually associated with a golem (in Jewish folklore, a golem [sometimes pronounced *goilem*] is an animated being crafted from inanimate material; the name appears to derive from the word *gelem*, which means ''raw material''). However, after a short time, the homunculus turned on its creator and ran away. The recipe consisted of a bag of bones, sperm, skin fragments, and hair from any animal of which the homunculus would be a hybrid. This was to be laid in the ground surrounded by horse manure for 40 days, at which point the embryo would form.[1]

The Greeks, including Hippocrates, pondered heredity. They devised a theory of ''pangenesis,'' which claimed that sex involved the transfer of miniaturized body parts: ''Hairs, nails, veins, arteries, tendons and their bones, albeit invisible as their particles are so small. While growing, they gradually separate from each other.'' This idea enjoyed a brief renaissance when Charles Darwin, desperate to support his theory of evolution by natural selection with a viable hypothesis of inheritance, put forward a modified version of pangenesis in the second half of the nineteenth century. In Darwin's scheme, each organ—eyes, kidneys, bones—contributed circulating ''gemmules'' that accumulated in the sex organs and were ultimately exchanged in the course of sexual reproduction. Because these gemmules were produced throughout an organism's lifetime, Darwin argued any change that occurred in the individual after birth, like the stretch of a giraffe's neck imparted by craning for the highest foliage, could be passed on to the next generation. Ironically, then, to buttress his theory of natural selection Darwin came to champion aspects of Lamarck's theory of inheritance of acquired characteristics—the very theory that his evolutionary ideas did so much to discredit. Darwin was invoking only Lamarck's theory of inheritance; he continued to believe that natural selection was the driving force behind evolution but supposed that natural selection operated on the variation produced by pangenesis. Had Darwin known about Mendel's work (although Mendel published his results shortly after *The Origin of Species* appeared, Darwin was never aware of them), he might have been spared the embarrassment of this late-career endorsement of some of Lamarck's ideas.

Whereas pangenesis supposed that embryos were assembled from a set of minuscule components, another approach, ''preformationism,'' avoided the assembly step altogether: either the egg or the sperm (exactly which was a contentious issue) contained a complete preformed individual called a homunculus. Development was therefore merely a matter of enlarging this into a fully formed being. In the days of preformationism, what we now recognize as genetic disease was variously interpreted: sometimes as a manifestation of the wrath of God or the mischief of demons and devils; sometimes as evidence of either an excess of or a deficit of the father's ''seed''; sometimes as the result of ''wicked thoughts'' on the part of the mother during pregnancy. On the premise that fetal malformation can result when a pregnant mother's desires are thwarted, leaving her feeling stressed and frustrated, Napoleon passed a law permitting expectant mothers to shoplift. None of these notions, needless to say, did much to advance our understanding of genetic disease.[2]

Fetiform teratoma (homunculus) is a term that has been given to a rare form of teratoma that resembles a malformed fetus. There are very few reported cases in the English-language literature of this entity. Since the discovery of this well organized and highly differentiated mature cystic teratoma, there has been a lively discussion and fascination as to its pathogenicity. This tumor must be distinguished from fetus-in-fetu, a parasitic monozygotic twin usually found inside the body of a newborn or infant, and an ectopic pregnancy. In this report, we document a case of fetiform teratoma occurring in a 23-year-old primigravida.

CLINICAL HISTORY

A 23-year-old woman, gravida 0, presented initially with a chief complaint of dyspareunia. Her past medical history and surgical history were unremarkable. She had no allergies and was on no medications. Initial physical examination revealed a left adnexal mass.

Ultrasound imaging of the pelvis revealed a complex

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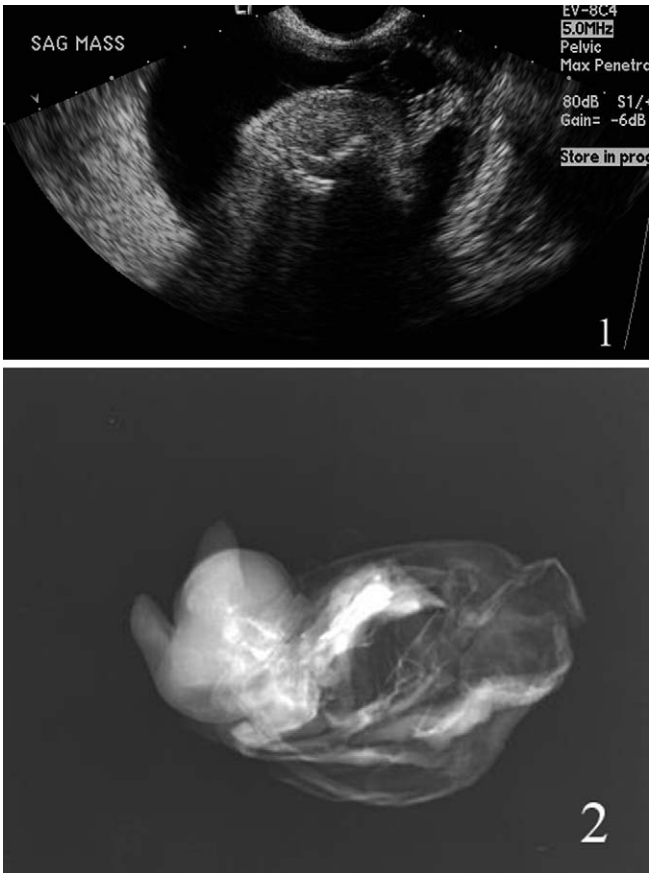

Figure 1. *Ultrasound of the pelvis demonstrating a complex cystic mass within the left adnexa that measured 9.9 × 9.8 × 9.0 cm.*

Figure 2. *Specimen radiograph demonstrating a 9.5 × 5.5 × 5.5 cm multilocular, thin-walled fluid-filled cyst.*

cystic mass within the left adnexa that measured 9.9 × 9.8 × 9.0 cm (Figure 1). It contained multiple septations and an echogenic nodule/mass within the left adnexa. The echogenic mass had shadowing suggestive of calcification. Magnetic resonance imaging of the pelvis revealed a 10.0 × 9.2 × 8.3 cm mass immediately anterior to the uterus and left ovary. The predominant component was low on T1 and high on T2 weighting, suggesting a cystic component. An irregular solid component within the primarily cystic mass was seen, measuring 4.4 cm in greatest dimension. The preoperative radiologic diagnosis was most likely an ovarian teratoma.

Laparoscopy was performed, but the mass was discovered to be too large to remove intact and a laparotomy was performed. At time of surgery, a heterogeneous mass was found attached to the left ovary.

GROSS PATHOLOGIC FINDINGS

Specimen radiograph examination revealed a 9.5 × 5.5 × 5.5 cm multilocular, thin-walled fluid-filled cyst (Figure 2). The cyst walls were smooth, gelatinous, and uniform throughout with a regular vascular pattern. Adherent to and within the cyst was a 6.5 × 4.0 × 3.0 cm fetiform structure covered with a viscous, sebaceous, keratinaceous-like substance (Figure 3). At its cranial pole was a 1.5 × 1.0 × 0.5 cm intact, membranous, clear fluid-filled cyst. Adjacent to the cyst were several thin, long, darkly pigmented hairs measuring 2.0 cm in length. The remainder of the fetiform structure was covered by skin bearing fine lanugo hair. A single rudimentary upper limb bud was present, measuring 1.5 cm in length. At the caudal portion were 2 rudimentary lower limb buds that included feet and toes. These measured 2.2 cm in length each. On the caudal portion cephalic to one of the limb buds was a 0.7 × 0.7 × 0.2 cm flesh-colored nodule covered by hair-bearing skin. Bivalving of the specimen revealed soft tan-yellow tissue. Centrally located was a 1.5 × 0.7 cm bony piece of tissue reminiscent of vertebral column. There was no grossly recognizable ovary, fallopian tube, placenta, or umbilical cord.

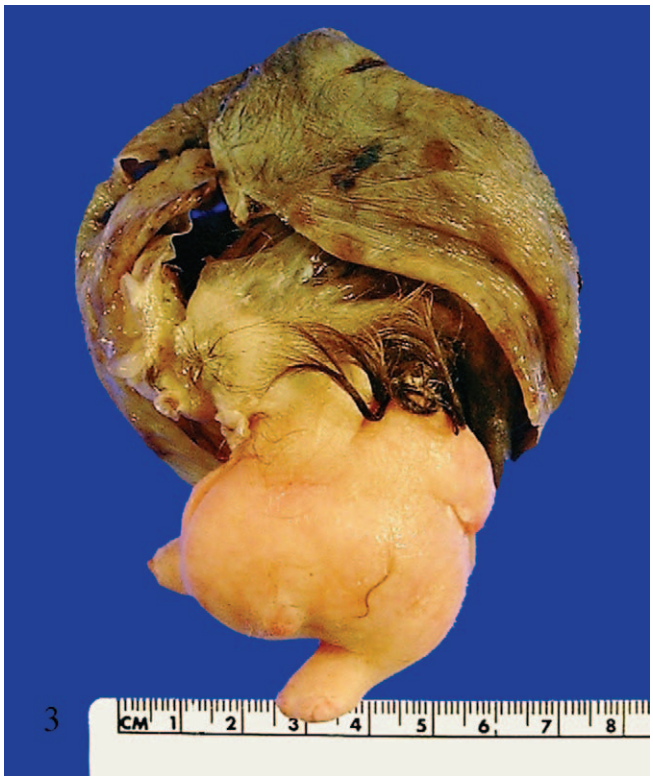

Figure 3. *Fetiform structure attached to cyst wall measuring 6.5 × 4.0 × 3.0 cm, covered with a viscous, sebaceous, keratinaceous-like substance.*

MICROSCOPIC PATHOLOGIC FINDINGS

Histologic examination revealed that the cyst walls were composed of a simple serous lining with 1 focus of squamous metaplasia and areas of denuded lining. There was residual ovarian parenchyma. The fetiform structure was covered in integument consisting of normal epidermis, collagen, and subcutaneous fat with underlying well-developed sebaceous and eccrine sweat glands and pilar structures. Tissues derived from ectoderm, mesoderm, and endoderm were identified. The limb buds and rudimentary digits consisted of rudimentary cartilage surrounded by fat, neurovascular bundles, and minute amounts of skeletal muscle with overlying skin (Figure 4, a). An epidermal inclusion cyst was identified. At the base of the skull, normal lamellar bone was present. Cartilage and bone that seemed to represent an immature nasal septum were present. An adjacent cyst was composed of respiratory epithelium, and sinonasal mucosa was present. There was also mature neural tissue present in the cranial

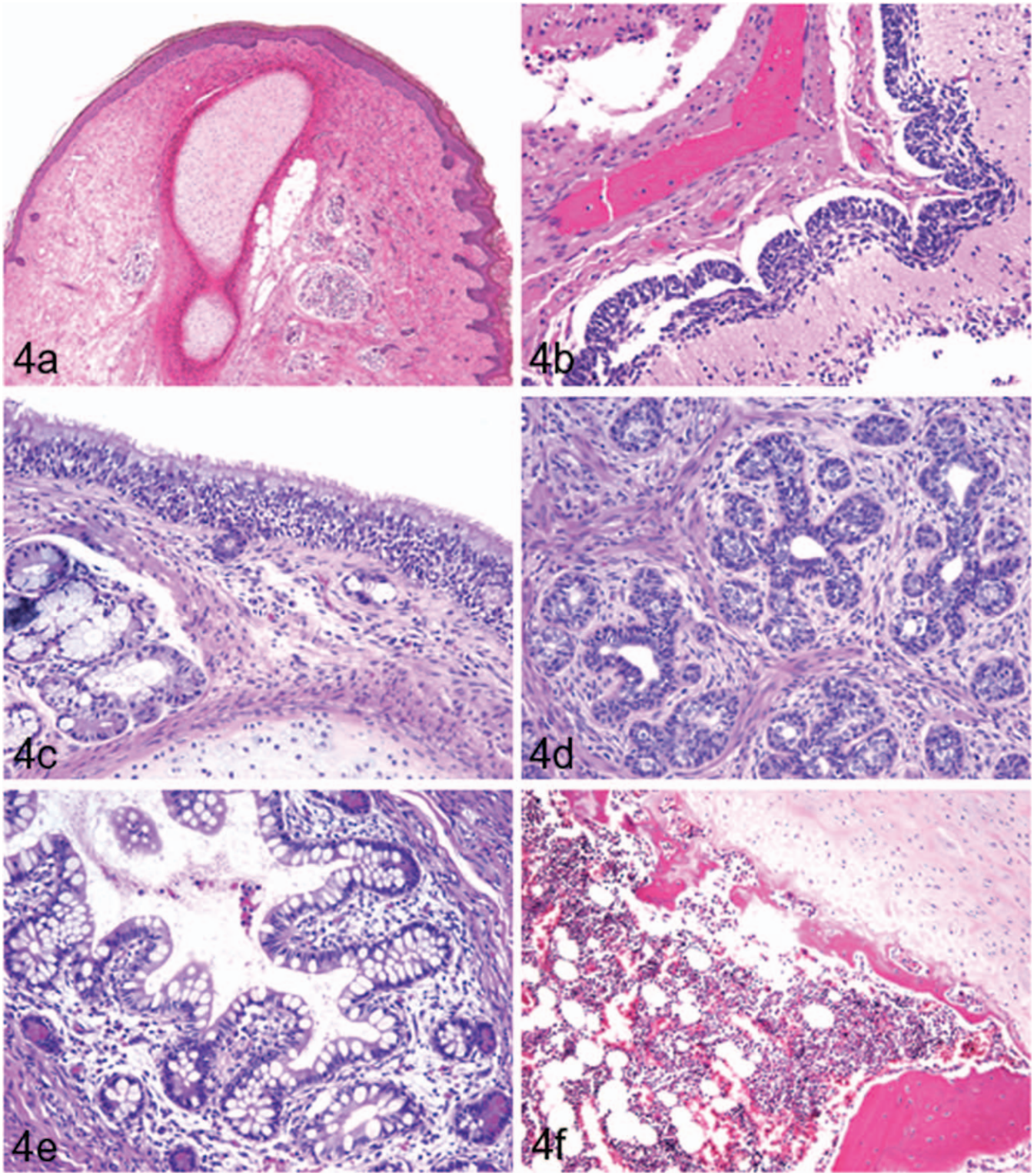

Figure 4. *a, Rudimentary digit (hematoxylin-eosin, original magnification ×100). b, Mature neural tissue resembling cerebellar folia (hematoxylin-eosin, original magnification ×200). c, Mature respiratory epithelium with underlying mucous glands and cartilage (hematoxylin-eosin, original magnification ×200). d, Fetal lung parenchyma (hematoxylin-eosin, original magnification ×200). e, Gastrointestinal mucosa (hematoxylin-eosin, original magnification ×200). f, Representative section of vertebral column with cartilage, bone, and normal bone marrow elements (hematoxylin-eosin, original magnification ×200).*

pole soft tissue with cerebellar folia (Figure 4, b) and choroid plexus. A ciliary body and retina were also identified. Other elements identified in the fetiform structure consisted of mature respiratory epithelium with underlying mucous glands and cartilage (Figure 4, c) and fetal lung parenchyma (Figure 4, d), as well as gastrointestinal mucosa (Figure 4, e). Thyroid tissue was identified. A representative section of the possible vertebral column demonstrated endochondral ossification with normal bone marrow elements (Figure 4, f). No immature elements and no placental membranes were identified.

COMMENT

Mature cystic teratomas are common benign ovarian tumors that occur most commonly in women of reproductive age. The majority are composed of disorganized, neoplastic, mature tissues of 1 or more of the embryonic germ layers: ectoderm, mesoderm, and endoderm. Despite the relatively benign nature of this neoplasm, there continues to be extensive research into this tumor because of its unusual development and fascinating ability to recapitulate any tissue found in the human body. Rarely, these tumors develop a high degree of differentiation and organization resembling a malformed fetus (fetiform structure).

We found 25 reported cases of fetiform teratoma in the literature. The age distribution of the patients ranged from 9 to 65 years.[3–7] However, most presented in the third or fourth decade of life. As was evident in this case, it is common that the caudal portion, including the lower extremities, of the fetiform structure is better developed than the cephalic portion. External sexual organ development, most often phalluslike, is not an uncommon finding.[3,4,7] A bony skeleton is typically present with varying degrees of limb formation, but visceral organ tissue and skeletal muscle are generally inconspicuous or absent. Ovarian teratomas are thought to arise from parthenogenetic development of a primordial germ cell.[9] This theory was supported by Linder et al[8], who employed cytogenetic and isoenzyme electrophoretic techniques to compare teratomatous and normal tissue. They demonstrated that teratomas are always homozygous, while normal tissues are heterozygous for chromosomal polymorphisms at or near the centromere. The authors concluded that mature cystic teratomas arise from a single germ cell that has completed the first meiotic division. Further support for this theory is that the anatomic distribution of this neoplasm is along the primordial germ line, and the age distribution is typically reproductive age.[10]

This entity needs to be distinguished from fetus in fetu. *Fetus in fetu* is a term first coined by Merkel in the 1800s.[11–14] It is a very rare congenital anomaly in which there is unequal division of totipotential cells of a blastocyst with the inclusion of these cells into the more mature embryo and is a form of a monozygotic diamnionic monochorionic twin pregnancy where the parasitic twin grows inside the body of its partner. The pathogenesis of this lesion is thought to be a consequence of embryonic duplication with anomalous inclusion of 1 twin in the body of a host twin occurring after anastomosis of the vitelline circulation, allowing 1 twin to parasitize the other.[12] Fetus in fetu has classically been distinguished from teratoma in that the diagnosis of the former requires the presence of a highly developed and segmented axial skeleton. This distinction is somewhat arbitrary but is based on the hypothesis that an axial skeleton implies development past the primitive streak stage, a stage thought to be too developed for teratoma.[12] Our case demonstrated a vertebral column, although it was not well developed. Besides a highly developed and segmented axial skeleton, organogenesis has also been mentioned as a distinguishing feature between these 2 entities.[3,4] A gastrointestinal system, central nervous system, genitourinary tract, respiratory system, and other less common organs including thyroid gland, liver, spleen, and lymph nodes have all been documented in fetus in fetu.[11–15] Interestingly, fetus in fetu almost always presents with acardia and anencephaly. In contrast, fetiform teratoma usually does not have complex, well-developed organs. However, Kuno et al[4] described a fetiform teratoma with both a highly developed axial skeleton and organs that included a brain, eyelike structure, trachea, thyroid gland, blood vessels, gut, and phalluslike structure that contained spongy vascular (cavernous) tissue. Remarkably, skeletal muscle has never been documented in a teratoma.

It has been proposed that fetiform teratoma and fetus in fetu can be differentiated based on zygosity.[4,9,16] As previously mentioned, most ovarian teratomas are homozygous at loci where the host normal tissue demonstrates heterozygosity, but fetus in fetu is genetically identical to its host. Cytogenetic examination was not performed on this case.

Clinically, ovarian fetiform teratomas and fetus in fetu present differently. Most reported cases of the latter have been discovered in infancy as an abdominal mass, and no case has been reported within an ovary.[14,15] The most common location is retroperitoneal, although cases have been reported in the skull, sacrum, mouth, and scrotum as well.[14,15] In contrast, fetiform teratomas are most commonly found in women of reproductive age and discovered as ovarian masses.[3]

Fetiform teratomas must also be distinguished from ectopic pregnancies. All reported cases of fetiform teratoma are composed of mature tissue and present without placental or trophoblastic tissue.[4] However, there have been 2 reported cases of umbilical cord structures described in fetiform teratomas, in which histologic evaluation was not performed.[4] A clinical history of an elevated β-human chorionic gonadotropin level and the documentation of chorionic tissue can substantiate the diagnosis of an ectopic pregnancy.

In summary, we have described a fetiform teratoma, a rare form of a mature cystic teratoma that is highly developed and organized, resembling a fetuslike structure. The degree of organization and differentiation can vary, blurring its distinction from either fetus in fetu or ectopic pregnancy. Its diagnosis requires both a clinical history and thorough pathologic examination. Cytogenetic/molecular studies may be helpful in distinguishing difficult cases.

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