Complications of Early Pregnancy and Gestational Trophoblastic Diseases

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Abstract

Placenta plays a crucial role in the development of the fetus. By connecting the fetus to the maternal circulation, it allows provision of oxygen and nutrients to the fetus while removing carbon dioxide and metabolic wastes. The placenta also provides essential hormones for the pregnancy and enables immunological protection for the fetus against infection and rejection by the maternal immune system. In this chapter, pathology of abortions as well as gestational trophoblastic diseases is discussed. Gestational trophoblastic diseases encompass a family of aggressive neoplasms, nonneoplastic lesions, and lesions with malignant potential that arise from various types of placental trophoblasts and may pose challenging problems in differential diagnoses in daily pathology practice.

Keywords

Pregnancy · ectopic pregnancy · hydatidiform mole · placental site nodule/plaque · exaggerated placental site · gestational trophoblastic neoplasia · choriocarcinoma · placental site trophoblastic tumor · epithelioid trophoblastic tumor

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13.1 Early Placental Development

13.1.1 Placenta Implantation

After fertilization of the ovum at the fallopian tube, morula and blastocyst are formed through cell division (Fig. 13.1). One week after fertilization, the blastocyst reaches the uterus. The proliferating and developing trophoblast cells then begin to adhere to a particular point and infiltrate through the endometrium (Fig. 13.2). The entire blastocyst is eventually embedded entirely in the endometrial stroma, i.e., implantation, 2 weeks after fertilization. The inner cell mass of the blastocyst will develop into embryo, yolk sac, amnion, and umbilical cord, while the outer trophectoderm will form placenta and chorionic membranes [1].

During implantation, the trophectoderm differentiates into an outer layer of mitotically inactive syncytiotrophoblasts and an inner stratum of mitotically active cytotrophoblasts. The fingerlike trophoblast processes permeate through the endometrium with formation of lacunae spaces within syncytiotrophoblast aggregates. The lacunae are then filled with maternal blood from uterine blood vessels eroded by the trophoblasts, forming the primitive uteroplacental circulation. At the same time, decidualization of the endometrium develops and provides immunological protection to the conceptus.

The primary chorionic villi develop by the end of second week from extensions of the proliferative cytotrophoblasts into the covering syncytiotrophoblast. This is followed by mesenchymal growth into such primary villi which are transformed to secondary chorionic villi that completely cover the surface of the chorionic sac. The tertiary villi then develop when the capillaries and blood cells grow from the villous mesenchyme. There is then establishment of blood flow between the embryonic heart and the villous capillaries by the end of the third week. Such connection enables exchange of oxygen, carbon dioxide, nutrients, and waste products between the maternal blood in the intervillous space and embryonic circulation in the villous capillaries. At the same

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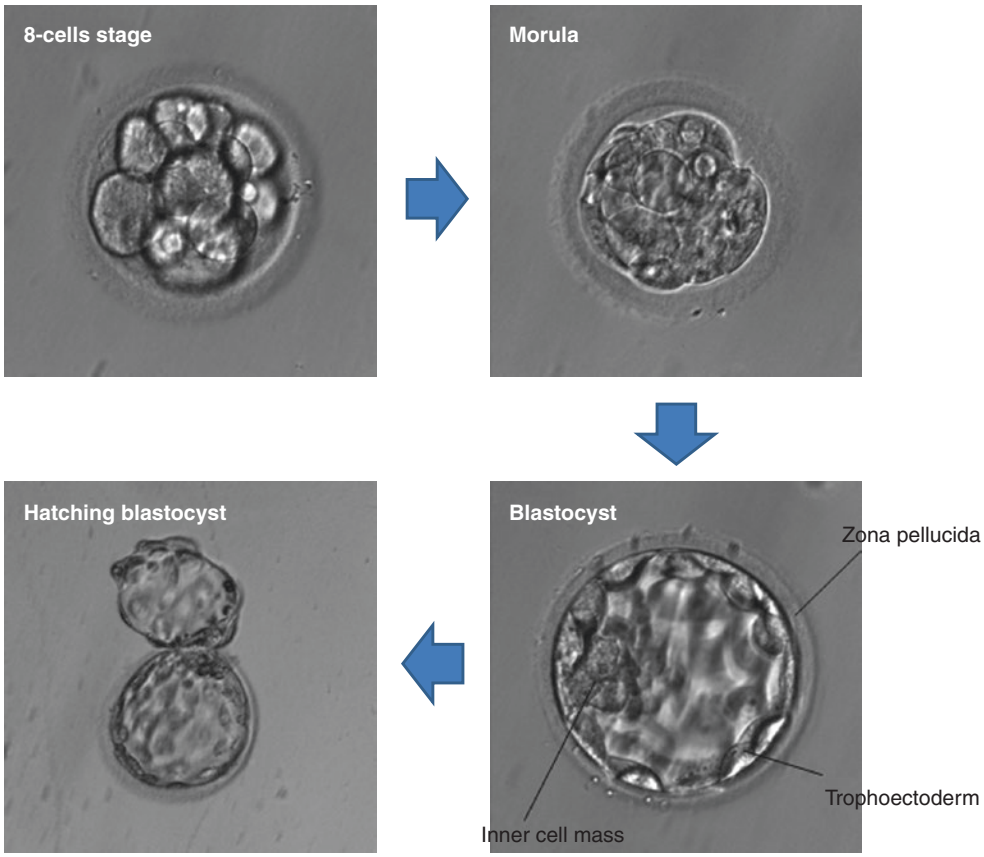

Fig. 13.1 Human embryonic development from 8-cell stage to blastocyst [contributed by Dr. Niu Ziru, Dr. Ye TM, and Dr. Philip Chiu, Department of Obstetrics and Gynaecology, the University of Hong Kong]

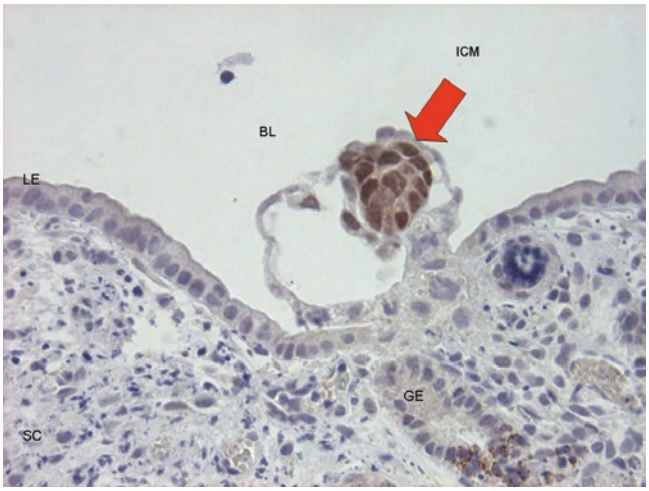

Fig. 13.2 Attachment of blastocyst onto endometrium in mouse. *LE* Luminal epithelium, *GE* Glandular epithelium, *SC* Stromal cells, *BL* Blastocyst, *ICM* Inner cell mass [contributed by Dr. Niu Ziru, Dr. Ye TM, and Dr. Philip Chiu, Department of Obstetrics and Gynaecology, the University of Hong Kong]

time, cytotrophoblastic shell is formed by the proliferative cytotrophoblasts that outspread the syncytiotrophoblast. Anchoring or stem villi are then formed with attachment to the endometrium through such cytotrophoblastic shells. From the stem villi, the branching terminal villi further develop to be surrounded by maternal blood in the intervillous space, allowing more efficient exchange between embryonic and maternal circulations.

13.1.2 Classification of Trophoblasts

Human trophoblasts can be categorized into cytotrophoblast, syncytiotrophoblast, and intermediate trophoblast according to the morphology and location of the cells [2–5] (Figs. 13.3, 13.4, and 13.5) (Table 13.1). Cytotrophoblasts are considered as precursors of intermediate trophoblasts and syncytiotrophoblasts. These cells are small and polygonal and with clear cytoplasm, distinct cell boundary, and a single, centrally located vesicular nucleus. Syncytiotrophoblasts are terminally differentiated mitotically inactive cells. They have amphophilic or eosinophilic cytoplasm and multiple small nuclei. Syncytiotrophoblasts are responsible for the production and secretion of human chorionic gonadotropin (hCG) and human placental lactogen (hPL). The histological features of intermediate trophoblasts are transitional between cytotrophoblasts and syncytiotrophoblasts. According to their locations, intermediate trophoblast is further subcategorized into the villous intermediate trophoblast at the core of the villous trophoblast columns; extravillous implantation site intermediate trophoblasts around the implantation site at endometrium; and extravillous chorionic intermediate trophoblasts at the chorion of placenta.

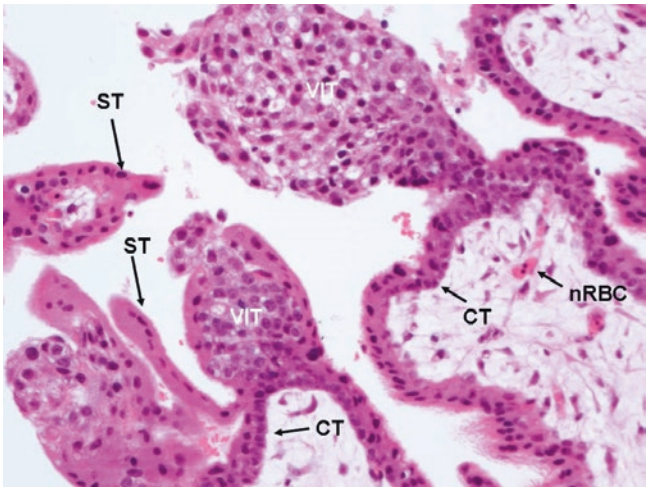

Fig. 13.3 Photomicrographs showing cytotrophoblasts (CT), syncytiotrophoblasts (ST), and villous intermediate trophoblasts (VIT) in the chorionic villi

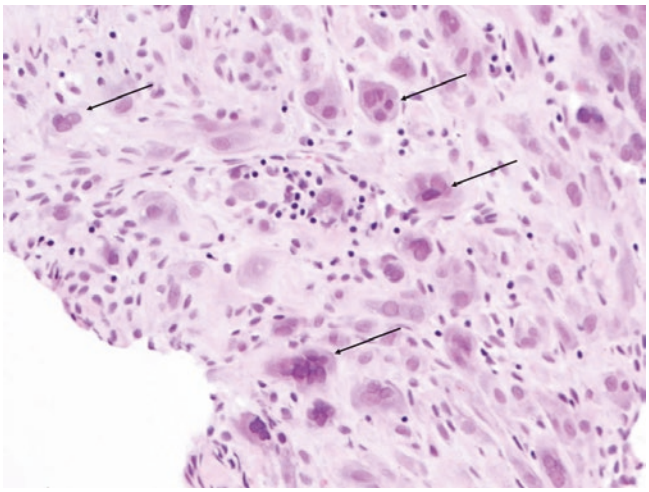

Fig. 13.4 Photomicrographs showing extravillous placental site intermediate trophoblasts (arrow) infiltrating the decidua physiologically

13.1.3 Biomarkers for Trophoblasts

Biomarkers for trophoblasts are useful both for clinical diagnostic purpose in routine pathology and in embryological research. The former supports existence of pregnancy at specific location while the latter helps to delineate cells of trophoblast lineage [6, 7] (Table 13.1).

In addition to traditional pregnancy-related hormone markers, such as hCG and hPL, more trophoblast biomarkers have been described recently, including inhibin-alpha, melanoma cell adhesion molecule (Mel-CAM or MUC18), histocompatibility leukocyte antigen G (HLA-G), HSD3B1, c-mos, and p63 genes [4, 5, 8–13]. Differential expression of individual marker in subpopulation of trophoblast exists.

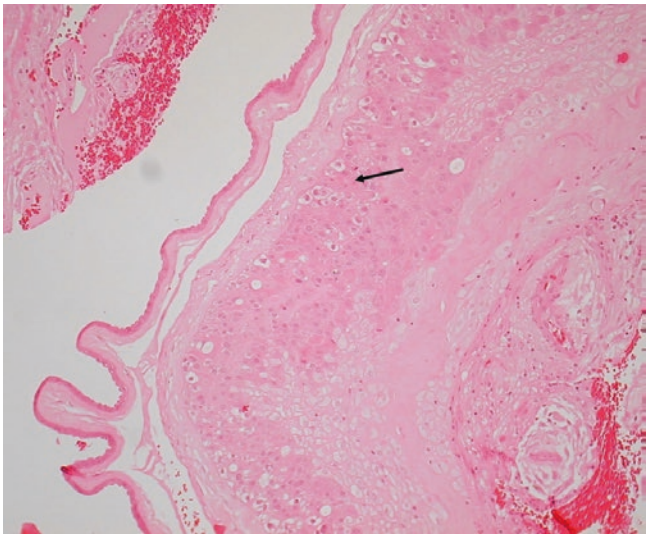

Fig. 13.5 Photomicrographs showing extravillous chorionic intermediate (arrow) at the chorion of placenta

In surgical specimens, particularly uterine curettings, it is important to demonstrate the existence of pregnancy products as evidence of intrauterine pregnancy and to exclude significantly the possibility of ectopic pregnancy. The application of cytokeratin immunohistochemistry, particularly cytokeratin 7, as well as sensitive and specific trophoblast markers is helpful in specimens where distinct chorionic villi or trophoblast cells cannot be found. Such trophoblast biomarkers are also useful in the differential diagnoses of trophoblastic lesions and non-trophoblastic pathology in the female genital tract; the latter includes various epithelial and smooth muscle tumors. This application will be further illustrated in subsequent sections on gestational trophoblastic diseases.

13.2 Challenges for Pathologists

Diagnosis and management of diseases related to early pregnancy need the close communication between pathologists and gynecologists. Differential diagnoses of the following issues are particularly important. (1) Spontaneous abortion: Pathologic examination is crucial in the confirmation of intrauterine pregnancy or indicating the possibility of ectopic pregnancy. The exact causes of abortion can be identified by histopathology in only a small proportion of cases, e.g., detection of cytomegalovirus infection (Fig. 13.6). (2) Ectopic pregnancy: The possibility of ectopic pregnancy should always be considered when samples from women of reproductive age group are examined. Timely diagnosis and management of ectopic pregnancy need the alertness and close collaboration of gynecologists and pathologists. (3) Hydatidiform mole or other trophoblastic tumors:

Table 13.1 Phenotypes of different types of trophoblasts [10]

	CT	ST	IT		
			Villous	Implantation site	Chorionic type
	Villous			Extravillous	
Morphology					
Shape	Round, uniform, small	Large syncytial	Polyhedral	Polymorphic and large	Round and polyhedral
Nucleus	Mononuclear	Multinuclear	Mononuclear	Mononuclear, occasionally multinuclear, nuclear membrane irregular	Mononuclear, occasionally multinuclear
Markers					
hCG	–	++++	–	–/+	–
hPL	–	+++	–/+	++++	–/+
Inhibin-α	–	+++	–	–/+	++
p63	+++	–	+	–	+++
Mel-CAM	–	–	–/++++	++++	–/+
PLAP	–	–/+	–	–/+	+++
c-mos	–	+++	++	–	–
HLA-G	–	–	+++	+++	+++
HSD3B1	–	+++	+/–	++	++
LESION					
Potentially malignant	Hydatidiform moles				
Malignant	Choriocarcinoma			Placental site trophoblastic tumor	Epithelioid trophoblastic tumor
Nonneoplastic				Exaggerated placental site	Placental site nodules and plaques

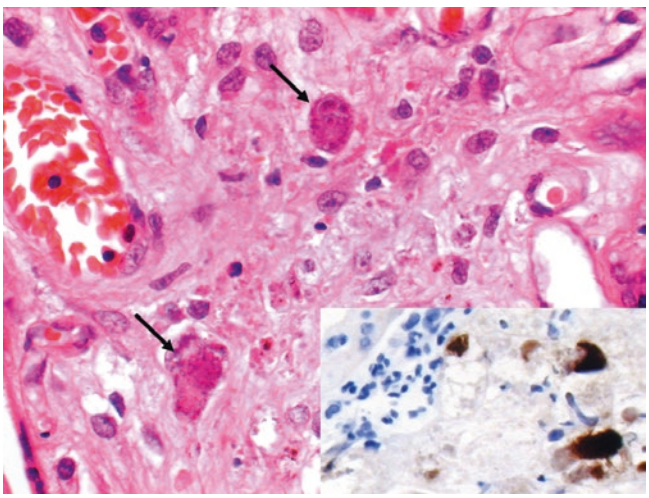

Fig. 13.6 Photomicrographs showing CMV inclusions (arrows) found at the chorionic villi of a case of intrauterine death. Immunohistochemistry confirms CMV antigens (inset)

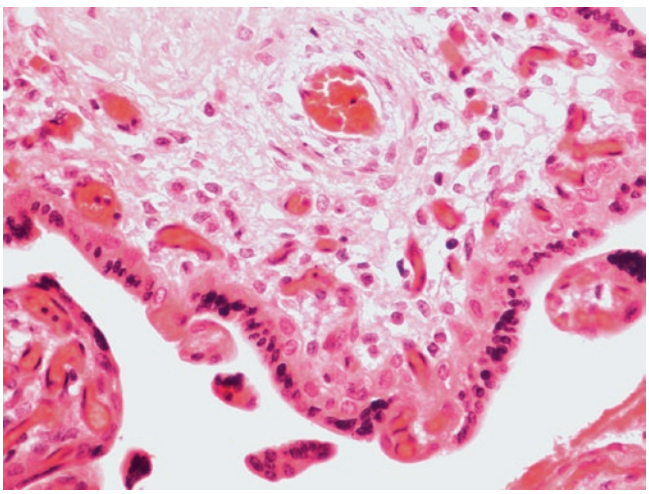

Fig. 13.7 Photomicrograph of a second-trimester placenta of a fetus diagnosed to have trisomy 21 during prenatal screening

13.3 Early Pregnancy Complications

13.3.1 Spontaneous Abortion

13.3.1.1 Clinical Features and Risk Factors

Spontaneous abortion refers to loss of pregnancy before the viability of the fetus is reached, usually by 24 weeks of gestation [14]. Most of the spontaneous abortions are sporadic. Recurrent abortion can be defined as the loss of three or more consecutive pregnancies (reviewed in [15]).

Karyotype abnormalities are the main causes of miscarriage in early pregnancy. The most common karyotype anomalies include trisomy (Fig. 13.7), X monosomy, and triploidy. Such abnormalities usually do not recur in future pregnancies.

Epidemiologically, maternal age and number of previous miscarriages are two major risk factors for predicting further

abortion. Environmental risk factors, such as smoking, alcohol, and obesity, have also been reported to increase the risk of recurrent abortions, although clear dosage-dependent evidence is conflicting. Maternal factors comprise conditions such as cervical incompetence and uterine abnormalities. The most treatable cause of recurrent abortion is probably the presence of antiphospholipid antibodies, including lupus anticoagulant leading to thrombotic diseases.

Genetic factors include chromosomal abnormalities of the embryo and the parents. It is estimated that chromosomal abnormalities of the embryo account for half of recurrent miscarriage. On the other hand, among 2–5% of couples with recurrent miscarriage, one of the partners may be a carrier of a balanced structural chromosomal abnormality, usually a balanced reciprocal or Robertsonian translocation [15].

In recent years, NLRP7 (NOD-like receptor, pyrin domain containing 7) gene of autosomal recessive heritage is found to be associated with recurrent hydatidiform moles or spontaneous abortions [16–18]. Placental abnormalities may be found in live or aborted fetuses associated with NLRP7 mutations [16].

Investigation on cytogenetic, anatomical, hormonal, immunological, and other abnormalities is usually not necessary for most cases of spontaneous abortions. On the other hand, women with a history of recurrent abortions should be managed in special clinics for professional management, including provision of the above tests, to provide guidance for management of subsequent pregnancies.

13.3.1.2 Macroscopic Examination of Abortion Specimens

Abortion placental tissue may be pale pink or greyish color with spongy or velvety appearance. If placenta or fetal parts can be identified macroscopically, sampling of placental tissue and decidua for histological examination is usually adequate. Otherwise, the entire sample should be embedded for histological examination. In particular, pathologists need to carefully check blood clot present for sac-like or transparent tissue within.

If vesicles are found during macroscopic examination or if clinical or ultrasound features are suspicious of hydatidiform mole, samples may be taken for flow cytometry or cytogenetic analysis in the fresh state. Prior discussion among gynecologists, pathologists, and experts specialized should be established for such practice. On the other hand, diagnosis and classification of hydatidiform mole can usually be achieved by morphological and immunohistochemical evaluation together with molecular pathology tests on formalin-fixed paraffin-embedded placental tissues nowadays.

13.3.1.3 Microscopic Findings

Pathological features: Edema and myxoid degeneration as well as villous fibrosis and sclerosis of the eventually avascular chorionic villi occur after death of the embryo (Fig. 13.8). If the villous edema is obvious (hydropic abortion), it is important to differentiate from hydatidiform mole and all the villi need to be sent for histological examination.

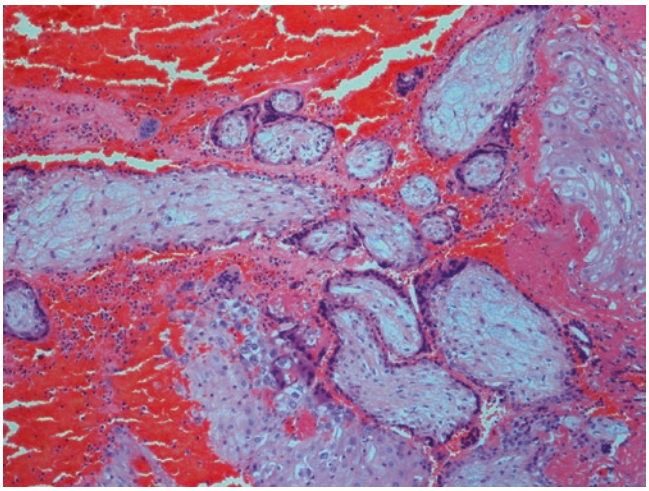

Fig. 13.8 Photomicrograph of a first-trimester spontaneous abortion with myxoid and fibrotic degeneration of chorionic villi

In contrast to hydatidiform mole, the villi from spontaneous abortion are usually regular in shape. Large villi or central cistern are rare. The villi may show hypovascularity or collapsed blood vessels. Fetal red blood cells may be identifiable. The trophoblast population is reduced. However, focal polar proliferation of cytotrophoblasts or villous intermediate trophoblasts may still be observed in some villi forming trophoblast columns.

In some cases, the causes of abortion may be identified through microscopic examination of the chorionic villi. For instance, morphological manifestations of viral infections (such as cytomegalovirus (Fig. 13.6) or parvovirus) may be detected. Occasionally, abortion caused by infection, such as group B streptococcus or Listeria, may exhibit severe acute inflammation of decidua as well as acute villitis. On the other hand, endometrial inflammation and necrosis is a common secondary change in spontaneous abortion and should not be regarded as evidence of infection-complicated pregnancy.

Fetal chromosome abnormalities such as trisomy may be associated with mild villous abnormalities and trophoblastic hyperplasia, but genetic analysis is necessary for diagnosis. Most abortion evacuation specimens contain placental implantation sites (Fig. 13.4). Sometimes, vigorous proliferation of trophoblast-infiltrating decidua and myometrium is present and may even display atypia. Pathologists must be aware that these are nonneoplastic physiological processes and misdiagnosis of trophoblastic tumor must be avoided.

13.3.2 Ectopic Pregnancy

13.3.2.1 Risk Factors and Clinical Manifestations

Ectopic pregnancy refers to the implantation of conceptus outside uterus or at unusual sites within the uterus. It occurs most commonly at the fallopian tube, followed by the ovaries, uterine cornu, cervix, vagina, and other organs. Tubal pregnancy occurs mainly at the ampulla, followed by isthmus and fimbria [14].

In recent decades, the incidence of ectopic pregnancy has increased significantly, from 0.4% to 1.6% according to some studies [19]. The risk factors include history of tubal surgery, sexually transmitted diseases, spontaneous or therapeutic abortion, pregnancy at advanced maternal age, use of intrauterine contraceptive device, as well as smoking. In addition, structural abnormalities of the fallopian tube including congenital defects, chronic salpingitis, recanalization after tubal ligation, as well as cilia dysfunction also increase the risk. Chronic salpingitis includes non-granulomatous (e.g., *Chlamydia trachomatis* and mycoplasma) and granulomatous (e.g., *Mycobacterium tuberculosis*) salpingitis.

It is estimated that 2–10% of pregnancies following assisted reproduction implant at the fallopian tube although the reason is unclear. It may be due to exogenous gonadotropin-induced secondary changes in hormone levels, or due to diseases underlying infertility [20]. The increased application of assisted reproduction may thus increase the incidence of ectopic pregnancy. Tubal inflammation with scarring and incomplete obstruction of the tube may also explain the increased incidence. Moreover, the increased sensitivity of imaging and laboratory technologies may have diagnosed early ectopic pregnancy that cannot be diagnosed in previous era.

Common symptoms of tubal pregnancy include abdominal pain and irregular vaginal bleeding, accompanied by history of amenorrhea. Some patients may develop shock due to intra-abdominal hemorrhage. However, one must bear in mind that atypical medical history and negative signs cannot completely rule out ectopic pregnancy. In particular, unruptured ectopic pregnancy may be painless with even absence of adnexal tenderness during examination. Positive pregnancy test supports diagnosis of pregnancy but cannot distinguish between abnormal intrauterine pregnancy and ectopic pregnancy.

13.3.2.2 Principles of Diagnosis

Ultrasound examination is helpful in the diagnosis of ectopic pregnancy and confirms intrauterine pregnancy. The diagnosis of intrauterine pregnancy can exclude ectopic pregnancy since coexisting intrauterine and ectopic pregnancies are extremely rare. Various options of management exist, including methotrexate and/or surgical treatment that comprise incision or excision of the fallopian tube. It has been reported that in cases when continued growth of residual incompletely removed trophoblasts infiltrated deeply in the muscle wall of the fallopian tube or other sites persistent pain and irregular vaginal bleeding with persistently raised hCG in blood and urine may result. This may be described as persistent ectopic pregnancy [21]. Ectopic pregnancy may occur, mainly in cases treated by non-radical surgery.

13.3.2.3 Pathological Examination of Excised Fallopian Tube

Macroscopic Examination

Fallopian tube excised for ectopic pregnancy should be examined for presence or absence of rupture and embryos. The fallopian tube may display variable degree of local or diffuse dilatation and serosal congestion. Blood clot and placental tissue may protrude from rupture. Pathologist should check carefully whether there is amniotic sac or fetal tissue in the blood clot. If embryo or placental tissue cannot be identified at the ruptured site, the entire fallopian tube should be cut open for examination. Adequate number of blocks should be taken.

Microscopic Examination

Microscopic examination is important to identify chorionic villi at possible ectopic sites. If villi are absent, the presence of extravillous implantation-site intermediate trophoblasts can still confirm the diagnosis of ectopic pregnancy. The implantation-site intermediate trophoblast is often found at the smooth muscle bundles of the fallopian tube infiltrating to the serosa or replacing the blood vessel wall.

The villous morphology may be normal in tubal pregnancies. In some cases, villous morphological changes may occur, such as villous fibrosis, edema, and hydropic degeneration (Fig. 13.9). While one should bear in mind the rare possibility of ectopic hydatidiform mole and choriocarcinoma, avoiding overdiagnosis is equally important [22, 23]. Florid polar trophoblastic proliferation in association with hydropic villi as well as extensive aggregates of extravillous trophoblast may be found in tubal ectopic gestation. On the other hand, the absence of circumferential trophoblastic proliferation and conspicuous stromal karyorrhexis should shed doubt on the diagnosis of ectopic hydatidiform mole. Examination of all sampled tissue as well as adjunct immunohistochemical and molecular tests can usually allow proper diagnosis.

13.4 Gestational Trophoblastic Disease

Gestational trophoblastic diseases (GTD) include a spectrum of trophoblastic disorders with distinct morphology and clinical behaviors as well as origins from various trophoblast population (Table 13.1). They can be developed from tropho-

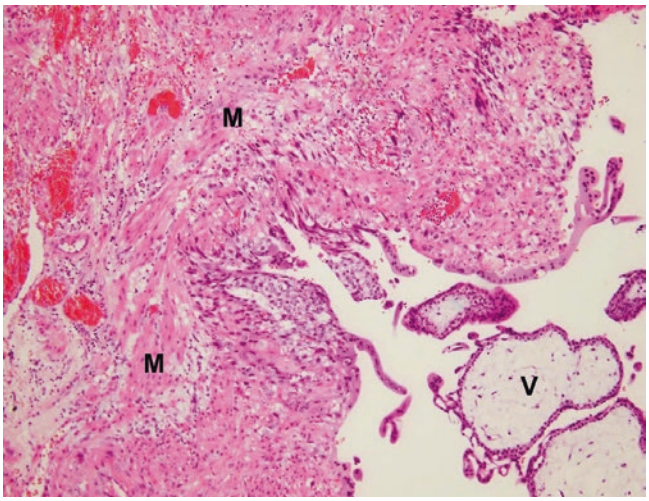

Fig. 13.9 Hydropic chorionic villi (V) in fallopian tube with trophoblasts impinging at the smooth muscle wall (M)

Table 13.2 WHO classification of gestational trophoblastic disease

Molar pregnancies	
	Complete hydatidiform mole
	Partial hydatidiform mole
	Invasive hydatidiform mole
Abnormal (non-molar) villous lesions	
Nonneoplastic lesions	
	Exaggerated placental site
	Placental site nodule and plaque
Neoplasms	
	Choriocarcinoma
	Placental site trophoblastic tumor
	Epithelioid trophoblastic tumor

blasts of the chorionic villi, implantation site, or chorion [13, 24], with close association with underlying chromosomal composition [4, 5, 24, 25]. They may be considered as transplants with pure or dominant paternal origin that invades the maternal body, sometimes in uncontrolled manner. Hydatidiform moles or molar pregnancies are the most common type of GTD) and the majority regresses after uterine evacuation. However, a small proportion of hydatidiform moles may develop persistently elevated serum human chorionic gonadotropin (hCG) in association with possibility of developing choriocarcinoma. Treatment therefore needs to be considered. Such cases are grouped under gestational trophoblastic neoplasia (GTN) cases together with the frankly malignant members of the GTD) family (Table 13.2) [26]. It is noteworthy that gestational trophoblastic neoplasia can occur after non-molar pregnancy, including spontaneous abortion, ectopic pregnancy, or even term pregnancy with live delivery.

13.4.1 Classification of Gestational Trophoblastic Diseases

GTD with major pathology at chorionic villi include complete hydatidiform mole, partial hydatidiform mole, and invasive hydatidiform mole. Recently, the term abnormal villous morphology (lesion) has been introduced to describe non-molar lesions with villous abnormalities simulating a partial hydatidiform mole [24]. Table 13.3 compares the clinical, pathological, and genetic features of these lesions [4, 5, 24].

In gestational trophoblastic neoplasms, chorionic villi are absent and these include choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor [24]. In exaggerated placental site and placental site nodules and plaques, nonneoplastic proliferation of extravillous trophoblasts occurs [24].

13.4.2 Epidemiology

Gestational trophoblastic disease has the highest incidence in African, Asian, and Latin American countries than in Caucasian societies. It is estimated that gestational trophoblastic disease occurs in 2–13/1000 pregnancies in Asia while the incidence in the United States and Europe is 0.5–1.84/1000 pregnancies [26–36]. It is noteworthy that there may be variations in the diagnostic definitions of hydatidiform moles and persistent trophoblastic disease. Moreover, some uterine curettings or tissue passed per vagina related to clinical diagnosis of missed abortion has not been sent for histopathological examination leading to underdiagnosis of hydatidiform mole. The incidence of choriocarcinoma is often difficult to appraise due to lack of diagnostic tissue biopsy to differentiate postmolar choriocarcinoma from invasive mole. It is reported to occur in around 1–9 in 40,000 pregnancies [37]. The incidences of PSTT and ETT are lower than choriocarcinoma.

The main factors associated with increased risk of gestational trophoblastic disease include maternal age of <15 or >40 years and a prior hydatidiform mole, although dietary and socioeconomical statuses have also been implicated [28, 30, 36, 38–41]. Indeed, it is observed that the incidence of hydatidiform moles in Asia has apparently been declining [42, 43]. Reduction in birth rates as well as improvement in diet and economy have been proposed to be the attributing factors.

13.5 Hydatidiform Mole

13.5.1 Complete Hydatidiform Mole

13.5.1.1 Genetic Composition

In complete hydatidiform mole, there is villous hydropic change with little or no fetal development. It is usually

Table 13.3 Similarities and differences between types of molar and non-molar diseases with hydropic chorionic villi [modified from [4, 5, 24]

	Complete mole	Early complete mole	Partial mole	Hydropic abortus
Clinical features	Second-trimester vaginal bleeding, high hCG levels	First-trimester missed abortion	Late first or early second-trimester missed abortion	Late first or early second-trimester missed abortion
Gross features	Large amount of tissue with prominent vesicles	Usually normal	Few vesicles, gestational sac may present	Small amount, may have gestational sac
Fetal parts	Absent	Absent	Present but may be abnormal	Usually absent
Villous population	Wide range of large and small hydropic villi	Mainly small hydropic villi	Two populations of hydropic and nonhydropic	Similar size
Villous shape	Round, bulbous	Prominent club-shaped stromal projections	Irregular	Round and smooth
Scalloped villous contour	Rare	Rare	Prominent	Rare
Trophoblastic inclusions	Common, irregular	Absent	Common, round	Occasional, single cell
Villous trophoblastic hyperplasia	Marked, circumferential, marked cytologic atypia	Mild, polarized, mild-to-moderate atypia	Mild, with trophoblast snouts. Focal mild atypia	Usually absent. If found, normally polarized. No atypia
Central cisterns	Common	Not prominent	Not prominent if in first trimester	Absent
Stroma appearance	Mucoid, bluish, no fibrosis	Mucoid, bluish, cellular with immature stellate cells	Nonhydropic villi are fibrotic, with ectatic blood vessels	Variable
Stromal karyorrhexis	Common	Prominent	Absent	Absent
Nucleated red blood cells	None	None	Present	Present
Extravillous trophoblasts	Hyperplastic, marked cytologic atypia, may show exaggerated placental site	Mild hyperplasia, mildly atypical	Normal, no atypia	Normal, no atypia
P57 immunostain	Negative	Negative	Positive	Positive
Ki-67 of cytotrophoblasts	High (>70%)	High (>70%)	High (>70%)	Low (<25%)
Karyotype	Diandric diploidy (46XX, 46XY)	Diandric diploidy (46XX, 46XY)	Diandric triploidy (69XXY, 69XXX)	Biparental diploidy (46XX, 46XY)

diploid (46, XX or 46 XY) with a paternal only genome [24, 44, 45] (Fig. 13.10).

13.5.1.2 Clinical Features

Patients usually present with second-trimester vaginal bleeding, and a large-for-dates uterus, accompanied by markedly elevated serum hCG levels [46]. There may be hyperemesis gravidarum and other symptoms related to preeclampsia, hyperthyroidism, and hyperreactio luteinalis [47, 48]. Rarely, there is vaginal passage of molar vesicles or manifestations related to metastases. In those presenting in the first trimester, there is usually an abnormal ultrasound scan with absence of fetal heartbeat [49]. The typical "snowstorm" pattern may not be well developed in such early cases and the clinical diagnosis is commonly a missed abortion [50, 51].

13.5.1.3 Pathological Findings

The classical appearance of grossly evident vesicles may not be readily appreciable especially if presentation is in the first trimester. When present, the vesicles are grapelike, semi-transparent, and of various sizes (Fig. 13.11). Some may reach 1 cm or more in diameter. The vesicles are often admixed with blood clot and decidua while normal placental or fetal tissues are not found, except in cases in which there is a concurrent twin pregnancy [52].

Histologically, the chorionic villi are irregular in shape and sizes. Some may be strikingly edematous (Fig. 13.12) while some may show club-shaped stromal projections (Fig. 13.13) [53, 54]. They may appear avascular, and enlarged with cistern formation. Numerous small blood vessels are usually present but they are more conspicuous with CD31 immunohistochemistry [55, 56]. Karyorrhectic debris is prominent and especially in early moles (Fig. 13.14) [46, 53, 55].

In first-trimester complete hydatidiform moles, the central cisterns may be small or absent. The villous stroma is pale to bluish in hematoxylin and eosin-stained sections (Fig. 13.15), and fibrosis is usually not a conspicuous finding. Intravillous trophoblastic inclusions are not common but may be seen. There is circumferential hyperplasia of the

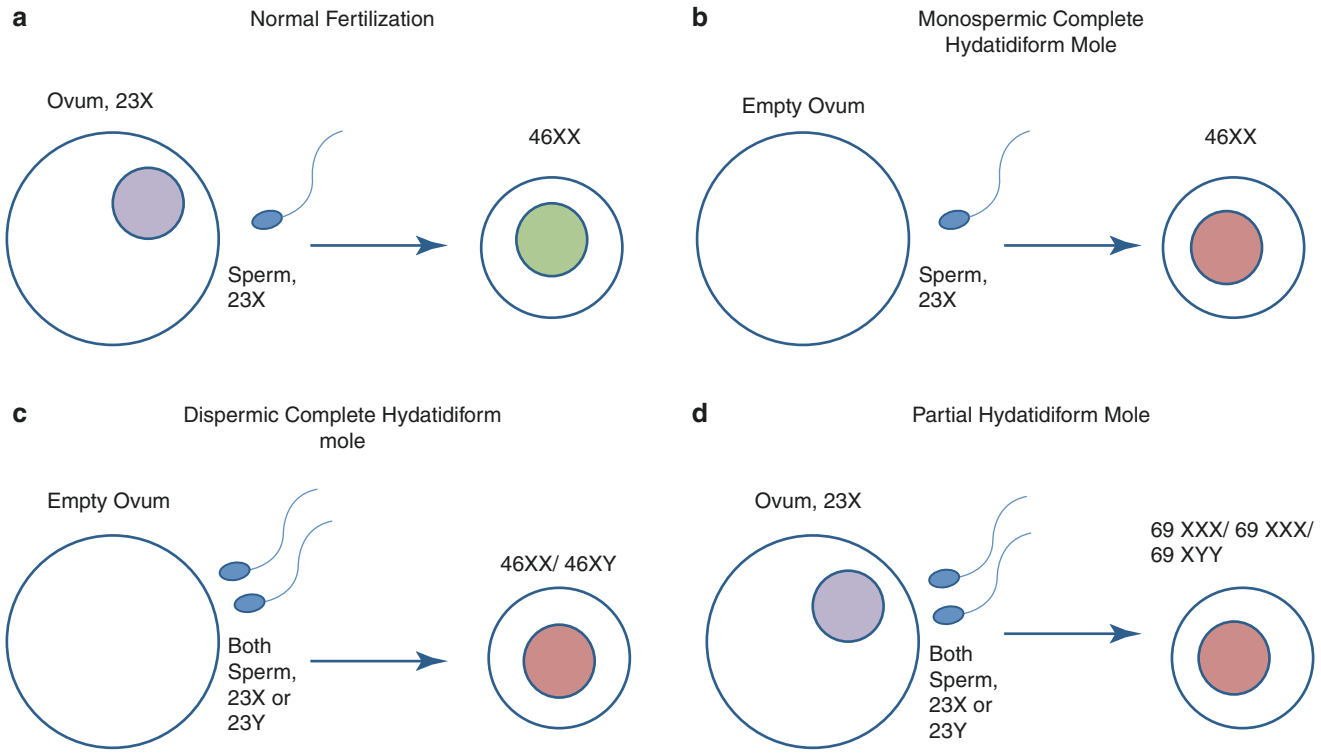

Fig. 13.10 Chromosome compositions in normal conceptus and hydatidiform moles. Normal fertilization involves fusion of one haploid chromosome from both the father and mother (**a**). Diploid chromosome composition is also seen in most complete moles. In monospermic complete mole (**b**), one sperm enters an empty ovum with no maternal chromosome and duplicates. In dispermic complete mole (**c**), two sperms enter an empty ovum and unite. In contrast, two haploid sets of paternal chromosomes fuse with an ovum with intact maternal haplotype to produce triploid genome in a partial mole (**d**) [47]

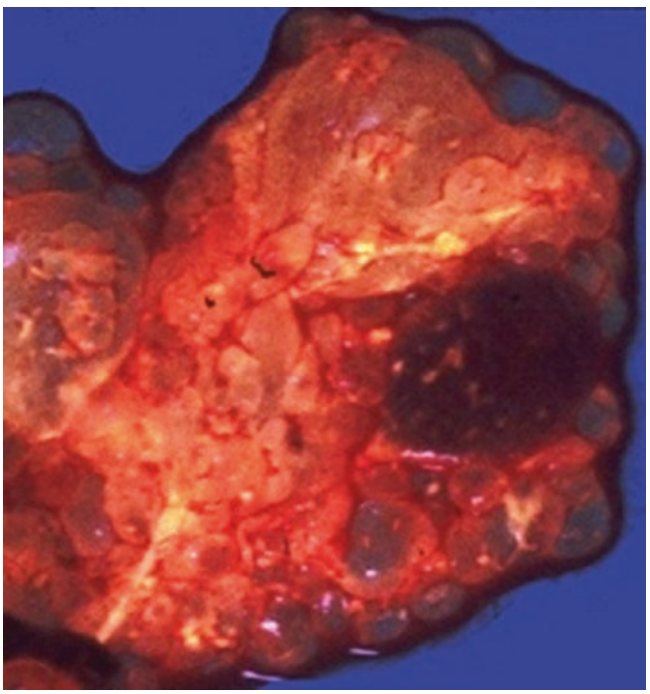

Fig. 13.11 Obvious vesicles are found in a case of complete hydatidiform mole

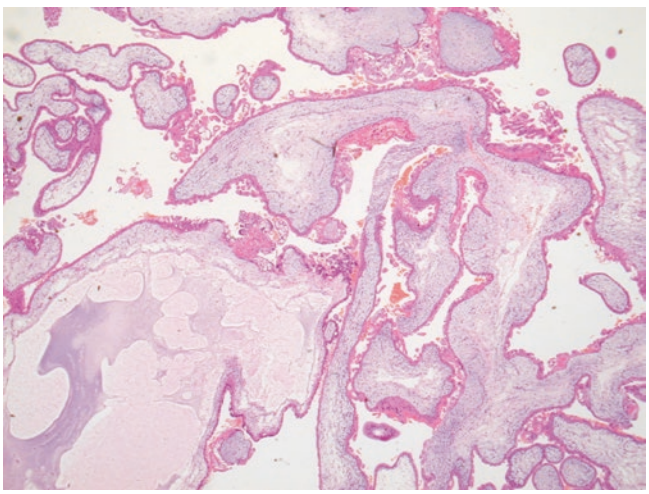

Fig. 13.12 Photomicrograph of a complete mole with prominent cistern formation and circumferential trophoblast hyperplasia

cytotrophoblasts, villous intermediate trophoblasts, and syncytiotrophoblasts. Syncytiotrophoblasts may contain cytoplasmic vacuoles and form lacelike projections from the surface. There is also marked proliferation of extravillous

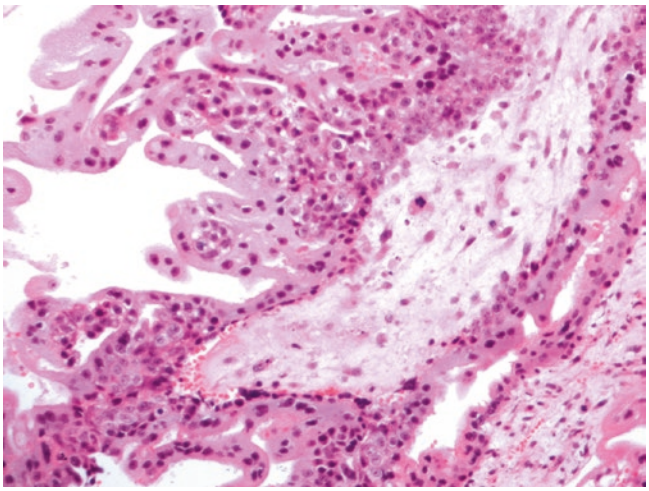

Fig. 13.13 Photomicrograph of a complete mole with club-shaped villi with florid trophoblastic proliferation

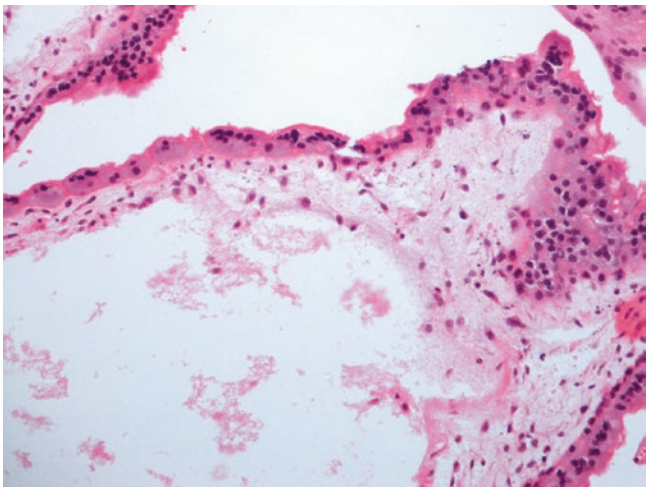

Fig. 13.14 Photomicrograph of a complete mole with cistern formation and apoptosis of stromal cells

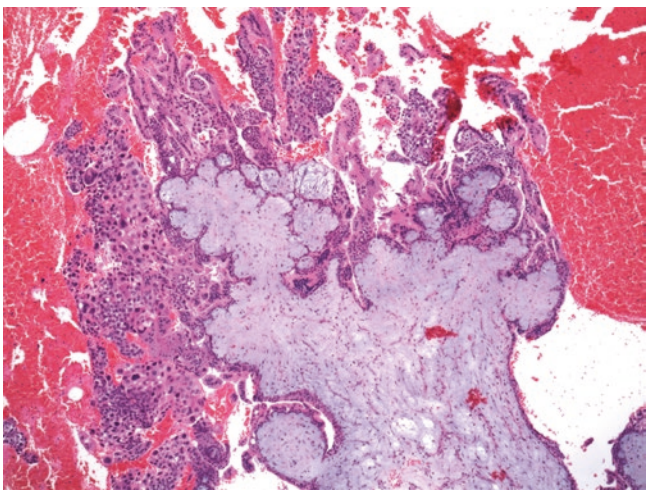

Fig. 13.15 Photomicrograph of an early complete mole with club-shaped villi and myxomatous stroma. Cistern formation is inconspicuous

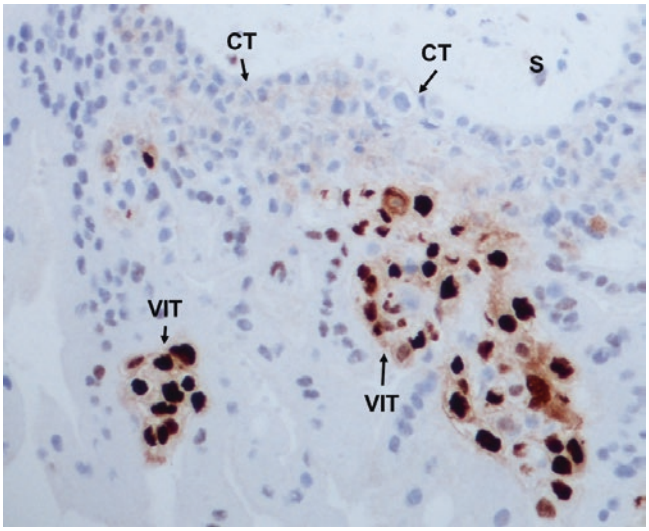

Fig. 13.16 The nuclei of the cytotrophoblasts (CT) and stromal cells (S) of this complete mole are negative for p57 immunoreactivity while the villous intermediate trophoblast (VIT) can be strongly positive

trophoblasts. The hyperplastic trophoblasts usually exhibit severe nuclear atypia and hyperchromasia, which is often apparent under low magnification. The degree of nuclear pleomorphism may be indistinguishable from that is seen in choriocarcinomas.

13.5.1.4 Biomarkers

The p57 immunohistochemistry is useful in confirming diagnosis (Fig. 13.16) [57, 58]. It has been shown to correlate with genotyping and can serve as a reliable marker for diagnosis of complete hydatidiform moles, as well as identifying mosaic conceptions [59]. The p57 is the protein product of the *cyclin-dependent kinase inhibitor 1C (CDKI1C)* gene (p57, Kip2) on chromosome 11p15.5, which is a paternally imprinted, maternally expressed gene. Lack of maternal chromosomes in complete mole renders the loss of expression in the villous trophoblasts and stromal cells. P57 immunoreactivity is usually retained in the villous intermediate trophoblast and implantation-site extravillous intermediate trophoblasts among decidua and may serve as an internal positive control. Almost all complete hydatidiform moles are p57 negative.

It is also important to be aware of aberrant p57 expression in some special scenarios. Rare cases of complete moles may show aberrant expression due to the retention of maternal copy of chromosome 11 such as in trisomies. In androgenetic/biparental mosaic/chimeric conceptuses (which may show either typical complete mole morphologies or absence of trophoblastic hyperplasia), there is discordant p57 expression with different expression profile in the villous cytotrophoblasts and stromal cells in same villi, i.e., positive immunoreactivity in cytotrophoblast but negative in villous stromal cells, or vice versa [59, 60]. Divergent

expression may also be seen in twin gestations, in which the p57 is absent in the villi of the complete hydatidiform mole but retained in those from the non-molar conceptus [61]. Familial biparental diploid products of gestation or complete moles related to *NLRP7* mutations may show variable levels of p57 expression and evidence of fetal development and mild trophoblastic proliferation resembling triploid partial mole. Such differential diagnosis should be kept in mind particularly in cases with a history of recurrent molar pregnancies.

Stromal apoptotic index has been shown to be higher in complete hydatidiform mole than in partial mole of normal placenta [56]. Overexpression of mRNA and protein of the transcription factor Nanog has also been shown to increase the risk of persistent gestational trophoblastic disease [62, 63].

13.5.1.5 Genetic Profile

Complete hydatidiform mole has a diploid androgenic only genome (two sets of paternal chromosomes) arising from fertilization of an empty ovum by one (monospermic) or two (dispermic) sperms (Fig. 13.10). In 80–90%, it is a result of fertilization of an empty ovum by one sperm (homozygous) and in 10–20% of an ovum by two sperms (heterozygous) with absence or subsequent loss of maternal chromosomes. Such absence of maternal alleles facilitates the diagnosis of complete moles using microsatellite analysis (Fig. 13.17). Mitochondria DNA of maternal origin, however, exists [64]. Rarely, they are tetraploid (containing four paternal haploid chromosomes, with a 92 XXXX karyotype) [44, 65–67].

Biparental Complete Moles

Rare cases of recurrent complete moles are biparental diploidy (as opposed to androgenetic diploidy) and are thought to be familial in origin. They have been shown to be related to maternal mutations in *NLRP7 or KHDC3L* (*C6orf221*) genes [16, 17, 68–70]. The mutations cause multiple epigenetic defects which result in the failure to establish maternal identity at imprinted loci and with abnormal expression of

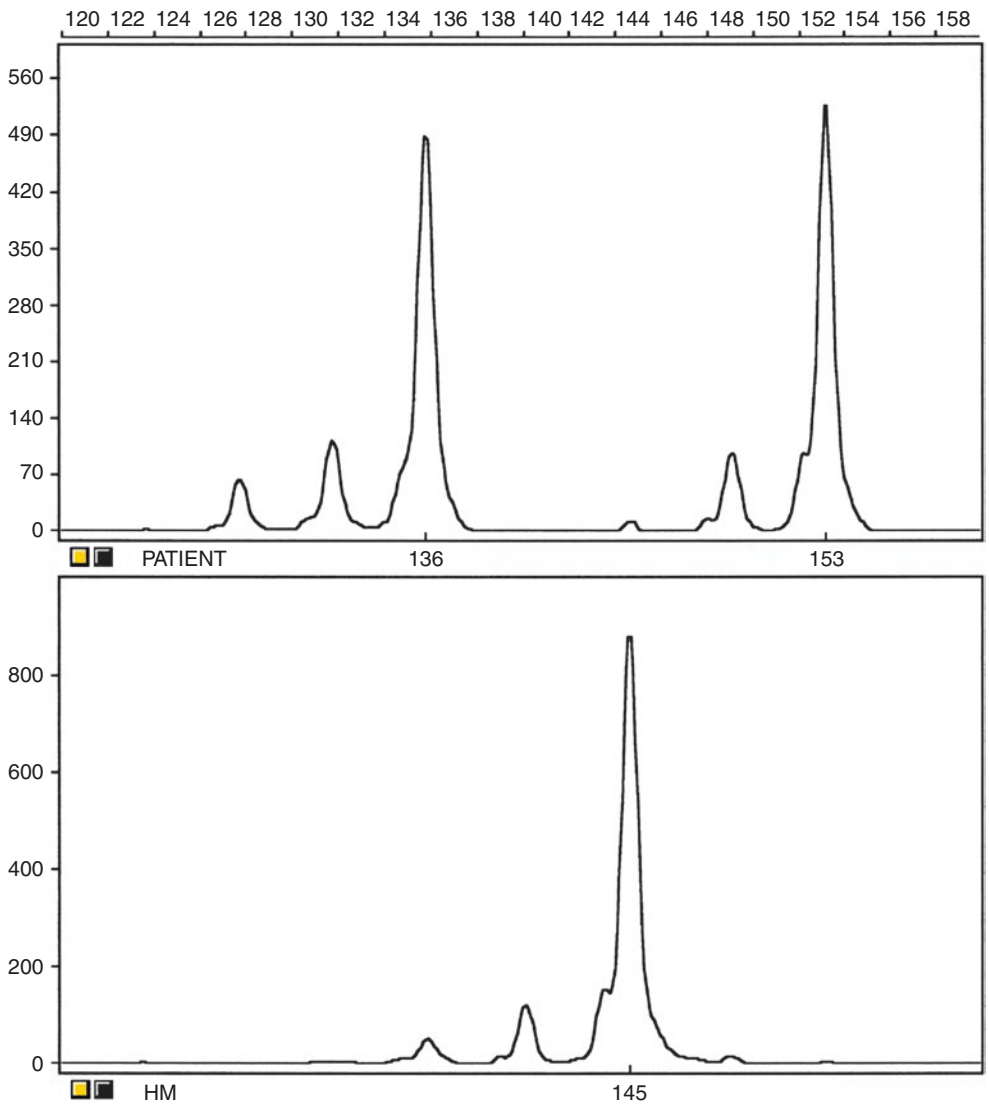

Fig. 13.17 Microsatellite polymorphisms of the decidua (upper panel) and villi (lower panel) of a case of complete hydatidiform mole. The patient is heterozygous for the marker generating alleles of 136–153 bp. The hydatidiform mole is homozygous giving rise to allele 145 bp

imprinted genes. It is estimated in a recent study that recessive *NLRP7* and *KHDC3L* mutations were found in 55% and 5% of patients with recurrent moles, respectively [69]. Genotyping of available molar tissues from these patients confirmed the diploid biparental contribution to all molar tissues from patients with recessive mutations in the known genes. Such genetic predisposition can be identified by appropriate genetic tests. Suitable genetic counselling and assisted reproduction may be provided in experienced centers. Live births (7–15% of pregnancies) have been reported among patients with recessive mutations and ovum donation was found to be helpful [71].

Indeed, in a study on products of gestations from patients with two defective NLRP7 alleles, all the conceptuses were found to be biparental diploid (Figs. 13.18 and 13.19). Variable p57 (KIP2) expression was found [70]. Positive p57 expression was found in cases with missense NLRP7 mutations and was strongly associated with the presence of embryonic tissues of inner cell mass origin and mild trophoblastic proliferation, features often considered supporting

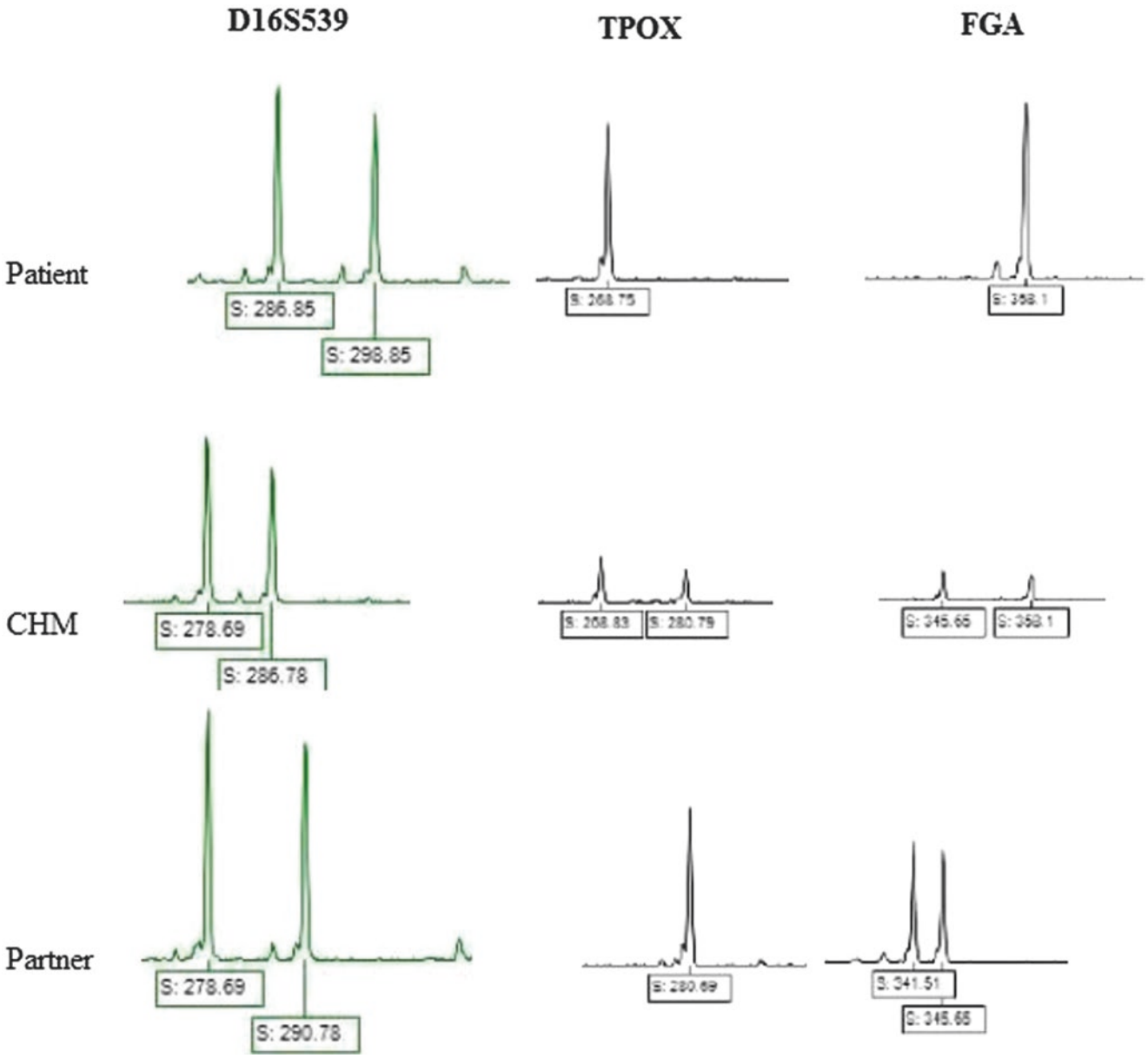

Fig. 13.18 Multiplex short tandem repeat genotyping results for a diploid biparental complete hydatidiform mole from a patient with biallelic mutations in *NLRP7*. Genotypes at three informative markers are shown and demonstrate at each of the three markers the presence of one allele inherited from the mother and another inherited from the father. For example, at marker D16S539, the complete mole received a 278 bp allele from the father and a 286 bp allele from the mother [contributed by Dr. Rima Slim, McGill University Health Center Research Institute Glen Site]

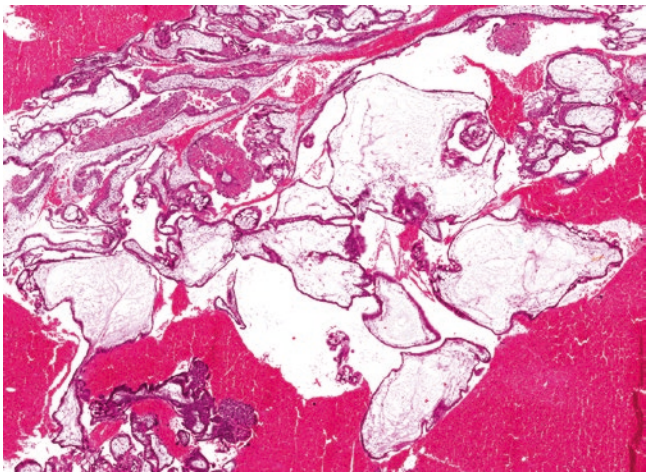

Fig. 13.19 Photomicrograph of a HM from a patient with diploid biparental biallelic NLRP7 mutations [contributed by Dr. Rima Slim, McGill University Health Center Research Institute Glen site]

diagnosis of triploid partial moles. In contrast, cases with protein-truncating NLRP7 mutations were negative for p57 (KIP2) expression and displayed florid trophoblastic proliferation with absence of embryonic tissues and excessive trophoblastic proliferation [70].

13.5.1.6 Differential Diagnosis

The differential diagnoses include early complete hydatidiform mole, and conditions in which there is abnormal villous morphology but have retained maternal genetic component. They include hydropic abortions, partial hydatidiform moles, trisomy 11, and placental mesenchymal dysplasia [25].

In early hydatidiform mole, central cisterns are not well developed. The hydropic villi usually have club-shaped stromal bulbous projections and the stroma is usually more hypercellular with many stellate cells, accompanied by striking stromal karyorrhexis [56]. There is a prominent labyrinthine network of villous stromal canaliculi. Trophoblastic hyperplasia is typically focal when compared with a second-trimester complete mole, and the process involves both villous surface and chorionic plate. Cytologic atypia is apparent even at this early stage [53]. The loss of p57 immunoreactivity in the villous trophoblasts and stromal cells confirms the diagnosis of a complete hydatidiform mole.

Hydropic abortus and partial hydatidiform moles may have hydropic villi but they both lack the club-shaped stromal projections and stromal karyorrhexis of complete hydatidiform mole [53–55, 72, 73]. Although early abortus may show some degree of circumferential trophoblastic proliferation, they generally lack the nuclear atypia of a complete hydatidiform mole. The retained p57 immunoreactivity in both villous trophoblasts and stromal cells facilitates their diagnoses [58].

In trisomy 11, the histologic appearance may resemble a typical complete mole. However, the triplicated chromosome 11 (the same chromosome on which the *CDKI1C* gene is located) can result in retained expression of p57 [58, 74].

Placental mesenchymal dysplasia may be confused with hydatidiform moles since there are usually a population of hydropic villi with central cisterns. Unlike hydatidiform moles, the hydropic change in placental mesenchymal dysplasia usually involves the stem rather than terminal villi. The villous blood vessels are also thickened with fibromuscular hyperplasia. The p57 immunostain shows a discordant pattern and is expressed in the villous trophoblasts but not in the stromal cells. The fetus may be normal or shows features of Beckwith-Wiedemann syndrome [75, 76].

13.5.1.7 Prognosis and Outcome

Persistent gestational trophoblastic disease occurs in 15–20% of patients with complete hydatidiform moles in which the serum hCG failed to normalize after the initial uterine curettage [26, 31, 77]. It is noteworthy that hCG assays for monitoring of GTN should be able to detect all forms of hCG and may be different from those for routine pregnancy test [26]. In fact, negative pregnancy test has occasionally been reported in patients with GTD [78]. Residual molar villi are usually found in repeated curettages. The risk of persistent disease is higher in those with a maternal age of >40 years, previous molar pregnancy, pre-evacuation hCG levels of >100,000 mIU/ml, a markedly enlarged uterus, and the presence of hyperreactio luteinalis, preeclampsia, hyperthyroidism, or trophoblastic emboli [61]. Those having a heterozygous genotype may also have a higher risk [79]. Uterine curettage performed in the first trimester does not appear to help reducing the frequency of persistent disease, although metastatic disease and choriocarcinoma are less frequent.

Complete cure is usually seen either in patients who do not have metastasis, or only if the metastases are confined to the lungs or vagina, or when the serum hCG is <40,000 mIU/mL. Even for those who have more extensive metastases and hCG >40,000 mIU/mL, cure may be achieved in >80% of cases. The risk of subsequent choriocarcinoma was reported to be 2–3% although risk is as high as 13% in Asian populations (see under subsequent section on choriocarcinoma) [31, 80]. Rarely, minimally invasive and quiescent GTD has been described (defined as patients with elevated hCG who show a falling trend on follow-up). False-positive hCG assay needs to be excluded and the need of chemotherapy is controversial [81, 82].

Recurrent complete mole is defined by discovering a new gestational trophoblastic disease after a post-chemotherapy remission. Recurrent complete mole has been reported to

occur in 1–1.8% who has had a previous complete mole, and 10–18% who has had two complete moles [83, 84].

13.5.2 Partial Hydatidiform Moles

13.5.2.1 Definition

Partial hydatidiform mole shows diandric triploidy (one maternal and two paternal sets of chromosomes). They contain a mixture of normal-sized and enlarged hydropic chorionic villi with localized and mild degree of trophoblastic hyperplasia [75, 85, 86].

13.5.2.2 Clinical Features

Patients usually present with vaginal bleeding or missed abortion in the late first or early second trimester. The serum hCG is usually low or normal for gestational age [46, 51]. Preeclampsia may occur later than for a complete hydatidiform mole [87]. Ultrasound scan of the uterus may show small or normal for dates uterus, presence of a fetus, and focally cystic placenta [88].

13.5.2.3 Pathological Findings

Gross appearance is dependent on the age of gestation. First-trimester partial moles may be indistinguishable from normal pregnancies. In a well-developed case, there is usually a mixture of markedly hydropic vesicles and normal placental tissue (Fig. 13.20). The fetus and an intact gestational sac may be seen [75].

Histologically, there are two populations of hydropic and normal-sized chorionic villi (Fig. 13.21). The hydropic villi are at least two to three times larger than the normal ones

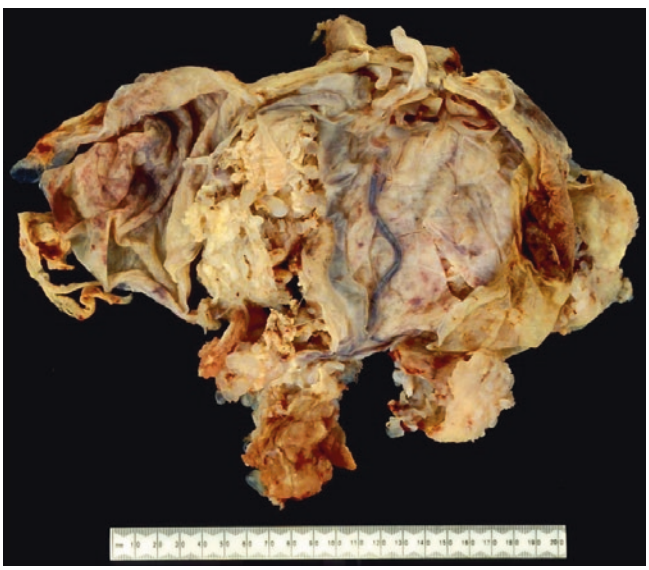

Fig. 13.20 Vesicles can be found in part of a placenta in this case of partial hydatidiform mole

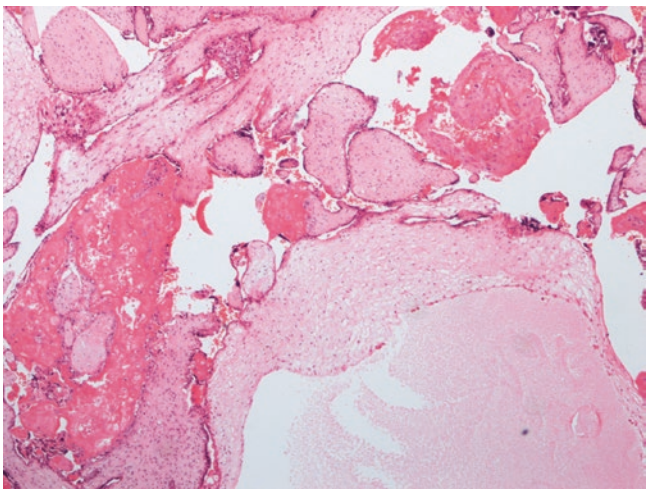

Fig. 13.21 Photomicrograph of a partial mole. Relatively normal-sized sclerosed villi and hydropic villi with cistern are both present

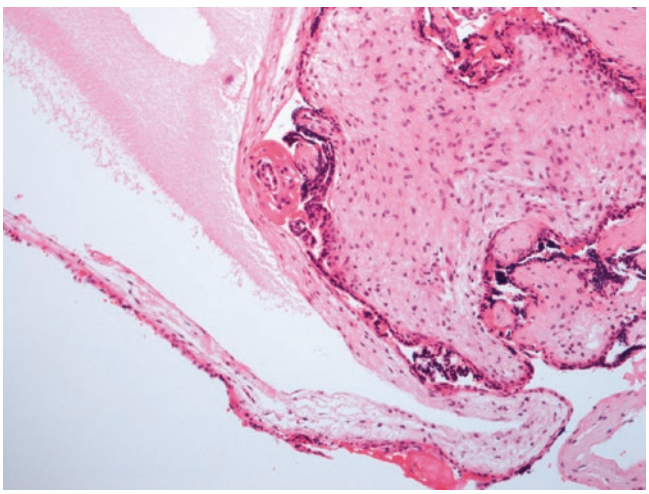

Fig. 13.22 Photomicrograph of a partial mole. Trophoblastic proliferation is mild

[75]. They show central cisterns but the frequency is less than that in complete hydatidiform mole. The villi are often irregular in shape, with scalloped borders and trophoblastic inclusions (invaginations of trophoblasts into the villous stroma). Trophoblastic hyperplasia is focal and mild compared with a complete mole (Fig. 13.22), and characterized by sprouts or knuckles of cells projecting from the villous surface. Circumferential hyperplasia is less common. The majority of hyperplastic cells are syncytiotrophoblasts and they quite often contain prominent cytoplasmic vacuoles and appear lacelike when the cells are arranged in sheets. In the villous stroma, there are fetal vessels containing nucleated red blood cells. Some of the blood vessels may appear ectatic. The normal-sized chorionic villi often have a fibrous stroma [54, 75]. The morphologic features of a classical partial mole may not always be present and may vary consider-

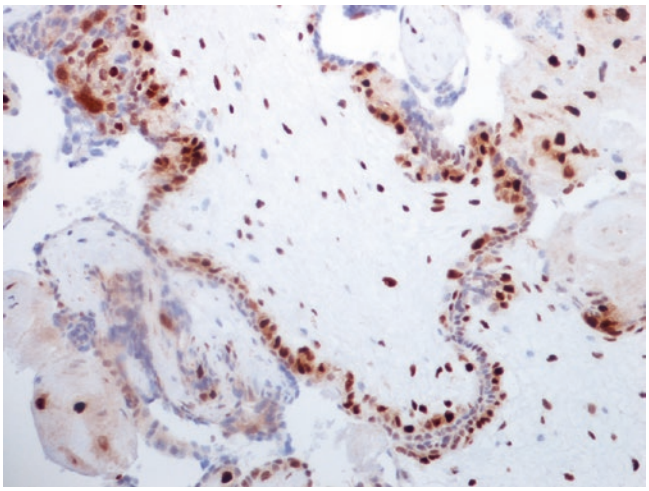

Fig. 13.23 The cytotrophoblasts and stromal cells of this partial mole are positive for p57 immunoreactivity

ably from case to case, and the appearance is dependent on the gestational age. For example, in early partial mole there may only be very few hydropic villi and the trophoblastic hyperplasia may be absent. Fetal tissue, chorionic and amnion membranes, and umbilical cord tissue may be present [72, 73].

13.5.2.4 Biomarkers

Although there is no specific immunohistochemical marker for diagnosis of partial hydatidiform mole, p57 is useful in the distinction from complete hydatidiform mole. In partial mole, the villous trophoblasts and stromal cells are immunoreactive for this marker (Fig. 13.23) [72]. The p57 immunoexpression is also retained in hydropic abortus and therefore this marker cannot be used to distinguish it from a partial mole [57, 58, 61, 85].

13.5.2.5 Genetic Profile

Almost all partial hydatidiform moles have a triploid karyotype [72, 73, 86] (Fig. 13.10). Most are 69XXY (70%), followed by 69XXX (27%), and the least common are 69XYY (3%) [86, 89]. Rarely, they are tetraploid in which there are three sets of paternal and one set of maternal chromosomes [90]. It should be noted that, while almost all partial moles are triploid, not all triploid conceptuses are partial moles (see under differential diagnosis below) [91].

13.5.2.6 Differential Diagnosis

The main differential diagnoses include entities in which abnormal chorionic villi are found. These are hydropic with or without other abnormal villous morphologies [25]. They include complete hydatidiform mole, hydropic abortions, gestations with chromosomal abnormalities, placental mesenchymal dysplasia, twin gestations, as well as familial biparental diploid POG/complete moles with missense *NLRP7* mutations.

Early complete hydatidiform mole may show immature hydropic chorionic villi without well-developed central cisterns (see under complete hydatidiform mole). Presence of fetal vessels and nucleated red blood cells, and retained p57 staining, will support a diagnosis of partial mole or hydropic abortion [72]. It has also been suggested that the MIB1 proliferative index (ki-67) in molar specimens is increased to >70%, in contrast to hydropic abortus which usually has an index of <25% [92]. For definitive diagnosis, DNA genotyping is the best method in distinguishing between molar and non-molar gestations [58, 93] (Fig. 13.24).

Even though the majority of abnormal conceptuses with a triploid karyotype are partial hydatidiform moles (with two paternal and one maternal sets of chromosomes), rare cases may be digynic triploid pregnancies (two maternal and one paternal sets of chromosomes) in which there may be abnormal villous morphology resembling a partial mole [73, 94]. Trisomies may show prominent trophoblastic inclusions or trophoblastic knuckles but these features may be inconsistently present. Cytogenetic studies and DNA genotyping would be useful for these cases [58, 66, 93].

13.5.2.7 Prognosis and Outcome

Persistent gestational trophoblastic disease occurs in 0.5–5% of patients with partial hydatidiform moles [61, 77, 95]. The persistent disease may be due to invasive mole and metastatic mole [96]. The risk of subsequent choriocarcinoma is <0.5% [80, 97].

13.5.3 Invasive Hydatidiform Mole

13.5.3.1 Definition

When there is the myometrial and/or vascular invasion by molar villi, or presence of metastases in extrauterine sites.

13.5.3.2 Clinical Features

Invasive hydatidiform moles occur in 5–10% of complete hydatidiform moles, in particular heterozygous/dispermic type [98]. Rarely do invasive moles follow a partial hydatidiform mole [96]. Patients with invasive hydatidiform mole usually have persistent vaginal bleeding and persistently high post-evacuation serum hCG levels, and repeat uterine curettage shows absence of any chorionic villi [99]. Distinction from choriocarcinoma is difficult.

13.5.3.3 Pathological Findings

Definitive diagnosis is made by finding of molar villi invading the myometrium and/or myometrial blood vessels (Figs. 13.25 and 13.26). Alternatively, the histologic

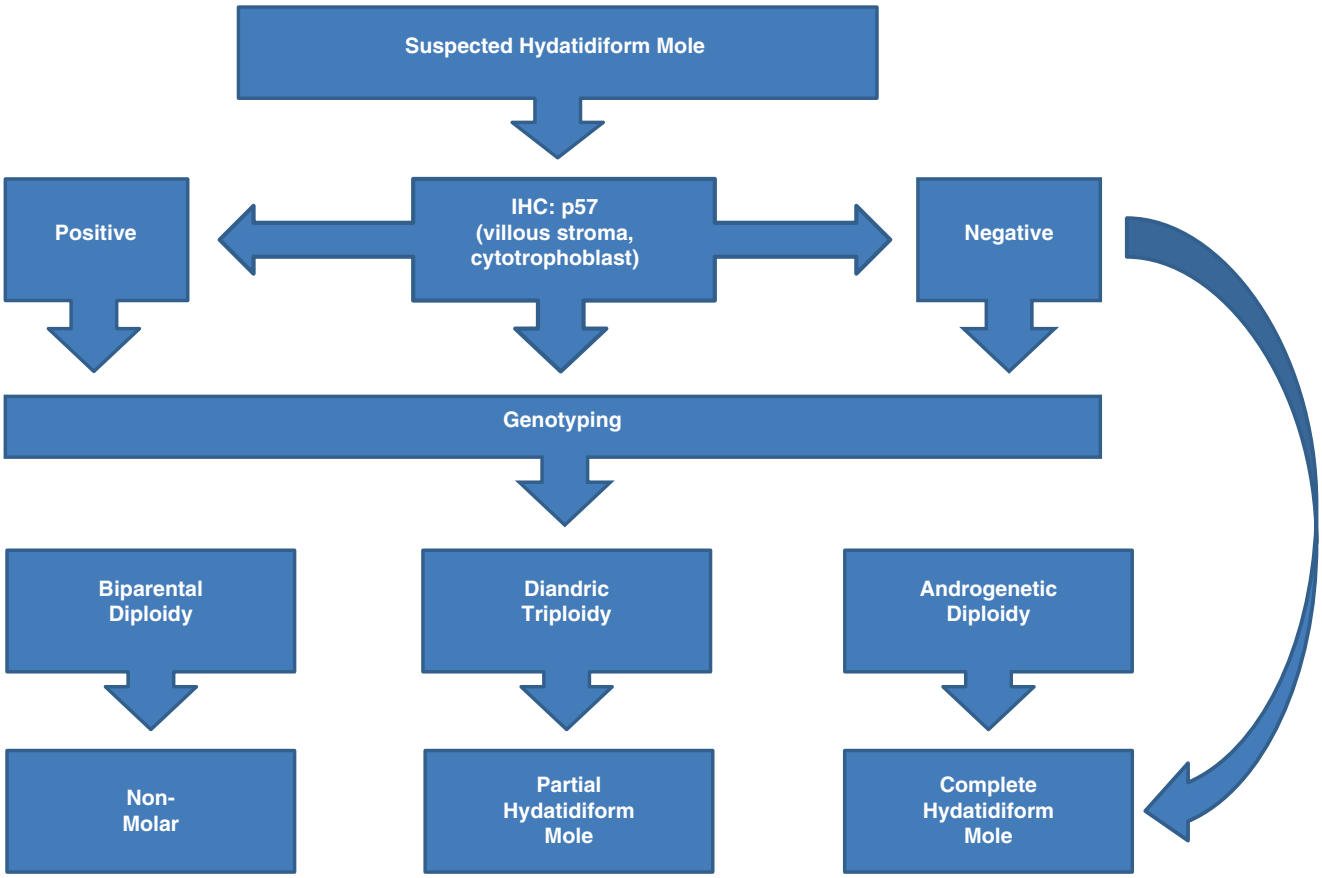

Fig. 13.24 Flowchart of diagnosis in cases suspected of hydatidiform mole [modified from Banet N et al. Mod Pathol 2014 [59]]

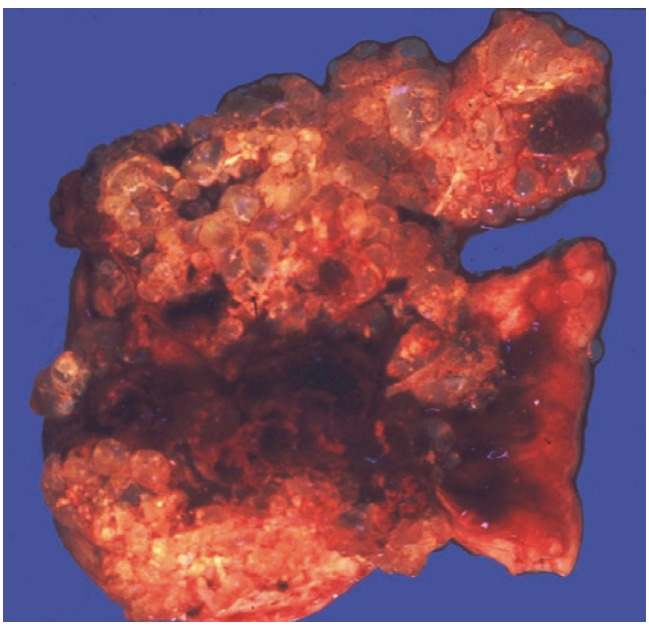

Fig. 13.25 Invasive mole. A uterus with extensive replacement by molar vesicles

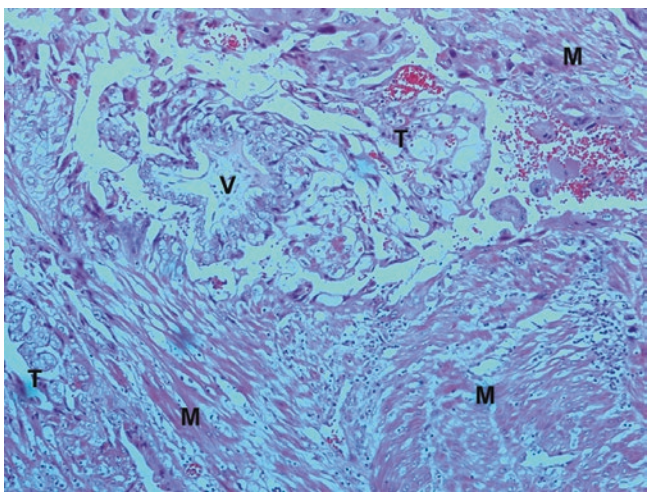

Fig. 13.26 Hydropic chorionic villi (V) with florid trophoblast proliferation impinging at the myometrium (M) of the uterus in this case of invasive mole

detection of metastases (with presence of molar chorionic villi) involving other pelvic sites (broad ligament, vagina, and vulva) and distant metastases (commonly in the lungs) would confirm the suspicion.

13.5.3.4 Differential Diagnosis

As most cases of clinical suspect invasive moles are not managed by hysterectomy, pathologic diagnosis is difficult. In repeat curettage specimens, a diagnosis of invasive mole cannot be made unless there is sufficient myometrium included to assess invasion.

In placenta accrete and increta, there is a normal placenta but it has implanted the myometrium without an intervening decidual layer. In these cases, the chorionic villi do not show the features of hydropic change or trophoblastic proliferation as seen in hydatidiform moles. If an invasive complete mole is suspected, a positive p57 immunostain would be useful.

13.5.3.5 Prognosis and Outcome

Invasive mole is often a clinical diagnosis. Patients usually have persistent elevated hCG levels but without residual molar tissue identified in the uterus on repeated curettage. These cases are considered persistent gestational trophoblastic disease or gestational trophoblastic neoplasia as it is usually not possible to distinguish invasive/metastatic mole from choriocarcinoma. Nonetheless, most patients are cured if treated with chemotherapy [24].

13.6 Specific Issues of Diagnosis and Management in Relation to Hydropic Villi

13.6.1 Hydropic Abortus and Abnormal (Non-molar) Villous Lesions

In routine surgical pathology practice, hydropic change of chorionic villi is a common finding in uterine evacuation samples. The challenge is to distinguish hydropic abortus from hydatidiform moles. There is significant interobserver and intraobserver variability in morphologic diagnoses even among experienced pathologists who subspecialize in gynecologic pathology [61, 73, 100]. Table 13.3 lists the similarities and differences between entities with problematic hydropic change.

From a practical standpoint, when hydropic change is identified in the initial sections selected for histology, all remaining tissue of the same specimen should be examined to exclude hydatidiform moles. All recent curettage specimens should also be reviewed. Application of p57 immunostain should help to exclude most cases of complete hydatidiform moles, with the exception of androgenetic/biparental mosaic/chimeric conceptuses and twin gestations (see under complete hydatidiform moles) [60]. In difficult cases in which the p57 expression profile is equivocal, molecular genotyping can be used to make a definitive diagnosis [57, 58, 66, 73, 93]. Hydropic abortus typically shows biparental diploidy, while complete and partial hydatidiform moles show androgenetic diploidy and diandric triploidy, respectively (see under complete and partial hydatidiform moles for rare exceptions).

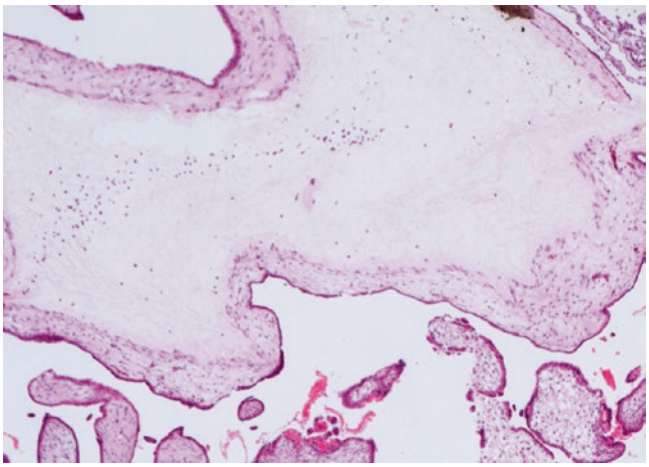

Fig. 13.27 Photomicrograph of a spontaneous abortion. The dilated stem villi may be misinterpreted as central cisterns

In a problematic hydropic abortus, the spectrum of villous abnormality may range from small, fibrotic villi to larger, hydropic villi, which can potentially mimic partial hydatidiform mole [72, 73, 75]. The chorionic villi in a hydropic abortus usually do not exceed two to three times the size of those of the background small villi and do not have typical central cisterns. It is important not to overinterpret dilated stem villi as central cisterns (Fig. 13.27). Another clue to support a hydropic abortus includes attenuated (rather than snouting) surface trophoblasts. Villous trophoblastic hyperplasia is commonly observed in non-molar abortuses with abnormal karyotype, such as trisomies, digynic triploid pregnancies, and placental mesenchymal dysplasia [72, 74, 75]. If molecular genotyping is not readily available, it is acceptable to sign out such cases as "abnormal villous morphology, features indeterminate for partial hydatidiform mole" (Fig. 13.28) [24]. These patients may be followed up for a short duration until the serum hCG is normalized.

13.7 Choriocarcinoma

13.7.1 Definition

Choriocarcinoma is a malignant gestational trophoblastic tumor in which there is simultaneous proliferation of intermediate, cytotrophoblasts and syncytiotrophoblasts of the chorionic villi.

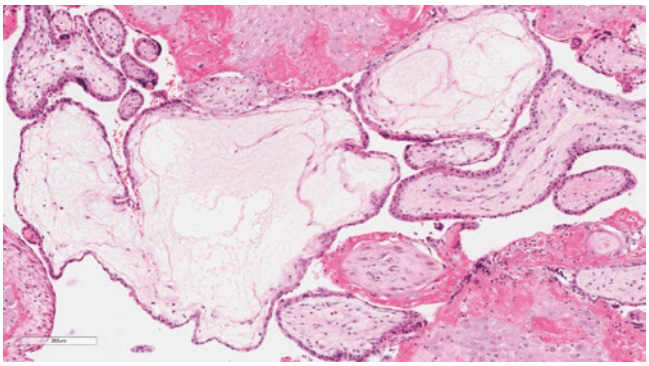

Fig. 13.28 A case that is being considered as having "abnormal villous morphology" with features indeterminate for partial mole

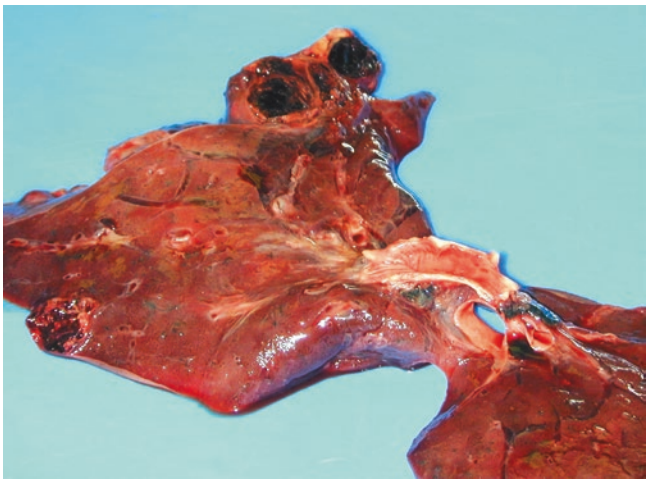

Fig. 13.29 Metastatic choriocarcinoma to the lung as hemorrhagic nodules

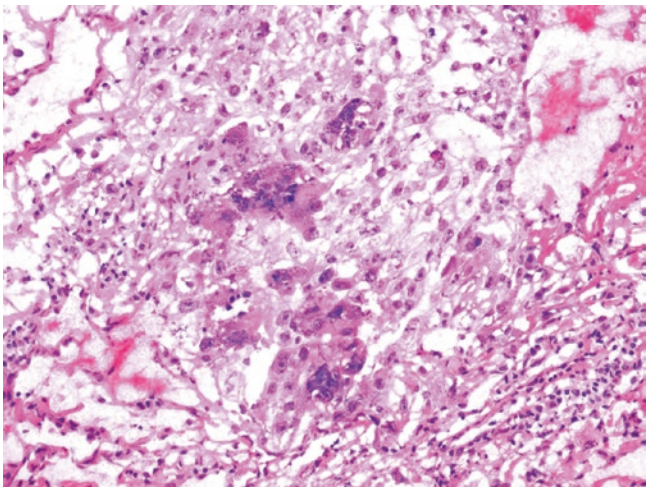

Fig. 13.30 Frozen section of a lung nodule reveals metastatic choriocarcinoma

13.7.2 Clinical Features

Choriocarcinomas are seen in women of reproductive age group, and rarely in teens and postmenopausal women [101]. They are two times more common in non-Caucasians than Caucasians with highest incidence reported in Asians, Africans, and Latin Americans [29, 102–109]. The usual presentation is abnormal vaginal bleeding or extrauterine hemorrhage and a highly elevated serum hCG level [101, 110]. The majority of choriocarcinomas (50%) are developed after a complete hydatidiform mole, an abortion (25%), normal pregnancy (22.5%), and ectopic pregnancy (2.5%) [50, 80, 97, 109, 111, 112]. The tumors usually develop after a latency of a few months to more than 14 years (with a mean of 13 months after a complete hydatidiform mole and a mean of 1–3 months after a normal pregnancy) [50, 80, 97, 101, 111]. The remainder of cases develop after a partial hydatidiform mole. The risk of post-molar choriocarcinoma is 2–3% and <0.5% for complete and partial moles, respectively. Rarely, the presentation is the incidental identification of a choriocarcinoma in a term placenta during microscopic examination [113, 114]. It is important to identify intraplacental choriocarcinoma for further investigation and follow-up due to the significant risk of metastasis in both the mother and baby.

13.7.3 Pathological Findings

Grossly, the tumor is typically hemorrhagic and alternates with fleshy and necrotic areas (Fig. 13.29). It may be large and involves both endometrium and myometrium with extension into cervix with extensive tissue destruction [115]. Ectopic sites include fallopian tubes and/or ovaries are uncommon [116, 117]. Histologically, the tumor grows in diffuse and infiltrating sheets and invades the myometrium or surrounding structures. The sheets of mononuclear intermediate trophoblasts and cytotrophoblasts are usually surrounded by multinucleated syncytiotrophoblasts in the periphery forming a biphasic and plexiform pattern (Figs. 13.30 and 13.31) [24, 110]. All the tumor cells show significant cytologic atypia and nuclear hyperchromasia, appreciable on low magnification. They have prominent nucleoli and are mitotically active. Some cells, especially the intermediate trophoblasts, may contain striking cytoplasmic clearing. Tumor necrosis and hemorrhage are often a prominent feature. In tumors treated with preoperative chemotherapy, the number of syncytiotrophoblasts may be proportionally less than intermediate trophoblasts and cytotrophoblasts but can be highlighted by hCG immunohistochemistry (Fig. 13.32) [118]. Rare cases of choriocarcinoma may contain a minor component of

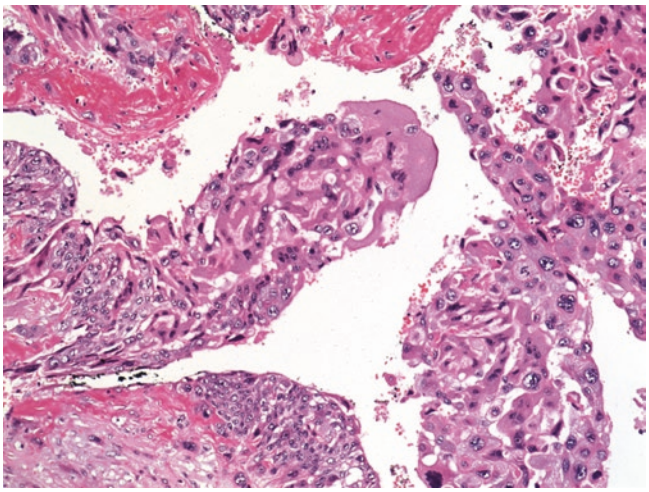

Fig. 13.31 Photomicrograph of a choriocarcinoma with plexiform pattern and coexisting mononuclear cytotrophoblasts and multinucleated syncytiotrophoblasts

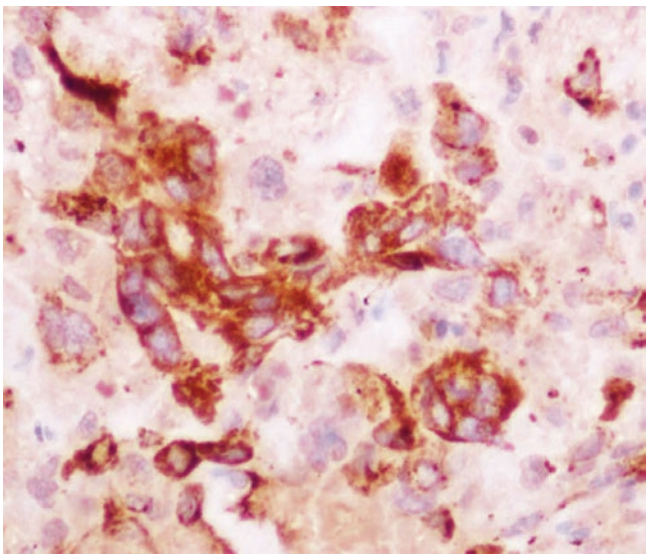

Fig. 13.32 The cytoplasm of syncytiotrophoblasts in choriocarcinoma are immunoreactive for hCG

placental site trophoblastic tumor or epithelioid trophoblastic tumor [119].

13.7.4 Biomarkers

All trophoblasts are stained with cytokeratins. The syncytiotrophoblasts are diffusely immunoreactive for hCG (Fig. 13.32), inhibin, and HSD3B1. The MIB1 proliferative index (ki-67) is >90%. The intermediate and cytotrophoblasts are immunoreactive for these markers but to a lesser degree. Intermediate trophoblasts also typically express hPL, Mel-CAM (CD146), HLA-G, and MUC-4. Cytotrophoblasts are typically negative for Mel-CAM [11, 12, 120–123].

13.7.5 Genetic Profile

The majority of choriocarcinomas have a XX sex chromosome composition [124]. Complex karyotypes with amplifications of 7q21-q31 and loss of 8p12-p21 have been reported [125, 126].

Recent genotyping study showed that gestational choriocarcinoma can be androgenetic or biparental [127]. Majority are androgenetic XX associated with CHM. Biparental choriocarcinoma, particularly those found postpartum, is related to intraplacental choriocarcinoma which may not be detected in routine examination (Fig. 13.33). Occasionally, androgenetic choriocarcinoma found with but separate from a coexisting intrauterine placenta may be due to dispermic twin pregnancy or originate from a pregnancy hydatidiform mole.

13.7.6 Differential Diagnoses

The differential diagnoses include other gestational trophoblastic tumors, non-gestational choriocarcinoma, high-grade carcinoma with trophoblastic differentiation, complete hydatidiform mole, and other nonneoplastic trophoblastic lesions [25, 128] (Tables 13.4 and 13.5).

Choriocarcinoma is distinguished from other gestational trophoblastic tumors, PSTT and ETT, by a very high serum hCG (choriocarcinoma which is much higher level than both placental site trophoblastic tumor and epithelioid trophoblastic tumor), presence of a distinctive plexiform growth pattern consisting of three cell types, and a MIB1 proliferative index >90%.

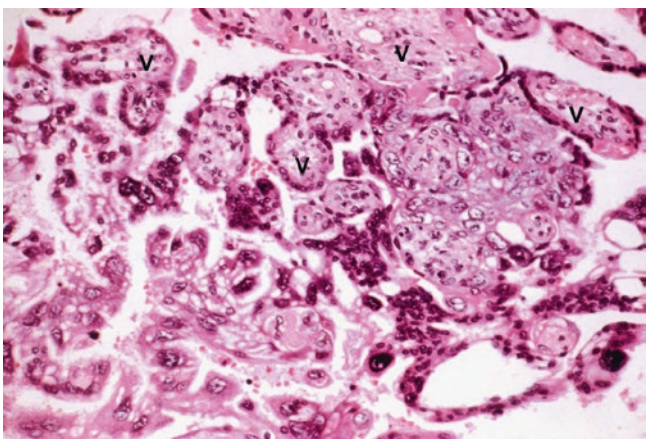

Fig. 13.33 Photomicrograph of an intraplacental choriocarcinoma extending from the villi (V) of a term placenta [contributed by Professor Harold Fox, University of Manchester]

Table 13.4 Histopathological characteristics of trophoblastic lesions

	EPS	PSN	CCA	ETT	PSTT
Discrete mass	–	–	+	+	+
Chorionic villi	+	–	–	–	–
Fibrinoid deposit	+	+	–	–	+
Vascular invasion	+	–	+	+	+
Extravillous trophoblast	+	+	–	+	+
Syncytiotrophoblast	+	–	+	–	–
Mitosis	–/rare	–/rare	+	+	+
Pan-cytokeratin	+	+	+	+	+
hCG	+	Focal +	+(ST)	Focal +	Focal +
hPL	+	Focal +	+(IT)	Focal +	+
α-Inhibin	+	+	+(ST)	Focal +	+
Mel-CAM	+	Focal +	+(IT)	Focal +	+
P63	–	+	+	+	–
Ki-67	<5%	<5%	>90%	10–25%	> 10%

EPS exaggerated placental site, *PSN* placental site nodule, *CCA* choriocarcinoma, *ETT* epithelioid trophoblastic tumor, *PSTT* placental site trophoblastic tumor

Table 13.5 Differentiated diagnosis of choriocarcinoma

	CCA	Other GTN (PSTT and ETT)	Non-gestational CCA (germ cell tumor)	High-grade carcinoma with trophoblastic differentiation	Complete hydatidiform mole
Serum hCG level	Markedly elevated	Mildly elevated	Markedly elevated	Mildly elevated	Markedly elevated
Chorionic villi	Absent	Absent	Absent	Absent	Present
Cell component	CT, ST, IT	IT	CT, ST, IT	Epithelial cell	CT, ST, IT
hCG stain	+++	+(Focal)	+++	+	+++

CCA choriocarcinoma, *GTN* gestational trophoblastic neoplasia, *PSTT* placental site trophoblastic tumor, *ETT* epithelioid trophoblastic tumor, *CT* cytotrophoblasts, *ST* syncytiotrophoblasts, *IT* intermediate trophoblasts

Pure non-gestational choriocarcinoma in the corpus is rare, and can be distinguished from gestational tumor by detailed reproductive history and DNA polymorphism analysis.

Identification of typical adenocarcinoma features elsewhere, a mild elevated of serum hCG, and limited hCG immunostaining facilitates the distinction of a poorly differentiated carcinoma with trophoblastic differentiation from choriocarcinoma [4]. Such ectopic hCG production has been reported in carcinomas of the lung and breast as well as melanoma and lymphoma [2, 3].

Trophoblasts in a complete hydatidiform mole may show striking nuclear atypia comparable to that seen in choriocarcinoma. Presence of hydropic villi, which may be scanty, supports a complete hydatidiform mole [58].

Nonneoplastic trophoblastic lesions may be encountered in small and limited uterine curettage samples and may result in diagnostic difficulty especially when a history of a prior pregnancy or abortion is unknown to the pathologist. Isolated degenerating trophoblasts without accompanying chorionic villi may be seen. The nuclei usually have a smudged appearance and there is often fibrin deposition (see subsequent section on placental site nodule and plaque).

13.7.7 Prognosis and Outcome

Choriocarcinomas are aggressive and have a propensity to metastasize to distant organs, commonly brain, lungs, and kidneys [129]. Disease duration greater than 4 months from delivery, pretreatment hCG level >100,000 mIU/mL, presence of liver, or brain metastases at diagnosis were among poor prognostic factors [31, 130, 131]. Nevertheless, with modern chemotherapy regimens, the prognosis has been drastically improved with cure achieved in >90% of patients [97, 108, 109].

13.8 Placental Site Trophoblastic Tumor

13.8.1 Definition

Placental site trophoblastic tumor is a malignant trophoblastic tumor of intermediate trophoblasts. The cell of origin is believed to be extravillous implantation-site trophoblasts [132].

13.8.2 Clinical Features

The affected women are usually in the reproductive age group (with a mean age of 30) and commonest presentation is abnormal vaginal bleeding but some may have amenorrhea or abdominal distention, simulating a normal pregnancy. Rarely, the presentation is that of a postmenopausal woman. An antecedent full-term pregnancy is found in more than two-thirds of women, with a median latent period of 18 months. The remainder follows a non-molar abortion or miscarriage [132–136]. Glomerular diseases including lupus nephritis are occasionally found in patients with PSTT [137, 138].

13.8.3 Pathological Findings

The tumor involves both endometrium and myometrium and presents as infiltrative masses ranging from 1 to 10 cm and cervical involvement is found in <10% of cases (Fig. 13.34). More than half of the cases invaded to outer half of myometrium and sometimes the serosa. The cut surface is usually fleshy, and alternates with white and yellow solid areas. There is often necrosis and hemorrhage but to a lesser extent compared with choriocarcinoma. Quite often, the diagnosis is made in a uterine curettage specimen (Fig. 13.35) and procedure-related perforation may occur in cases with almost full-thickness myometrial invasion. Microscopically, the tumor cells are arranged in sheets and dissect the myometrial smooth muscle bundles. The classical feature is an angiocentric-angioinvasive pattern of blood vessel wall involvement by groups of tumor cells. The involved vessels show fibrinoid change accompanied by tumor penetration into the vascular lumina (Fig. 13.36). Coagulative tumor necrosis and infarct-type necrosis are common. Most tumor cells are mononucleate and have polygonal shape, but some may appear spindle. A small number of cells may also be binucleate or multinucleate and it is important to distinguish from an under-sampled choriocarcinoma. The cells may have eosinophilic or clear cytoplasm. Nuclear pleomorphism is pronounced and pseudonuclear inclusions and nucleoli are prominent. The mitotic count is low with a mean of 5 per 10 high-power fields (Fig. 13.37). The background endometrium may show decidual change and/or Arias-Stella reaction [132, 136, 139].

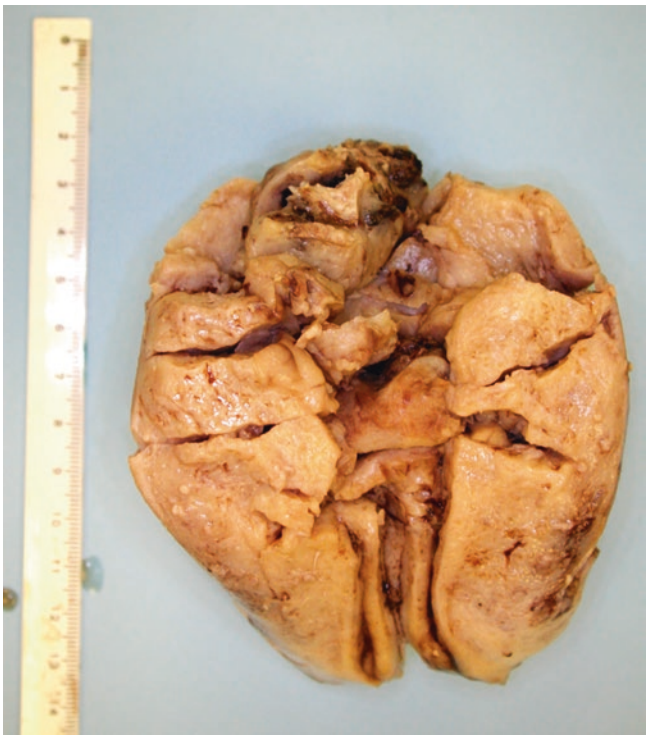

Fig. 13.34 Tumor nodules of PSTT found at resected uterus

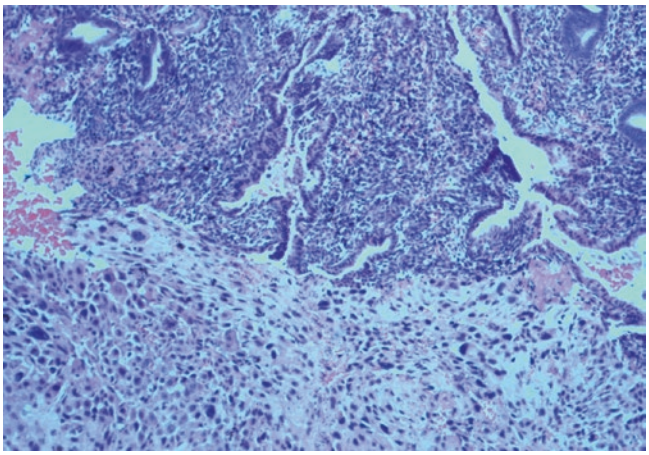

Fig. 13.35 Confluence mass of PSTT found next to pieces of endometrium in a uterine curetting

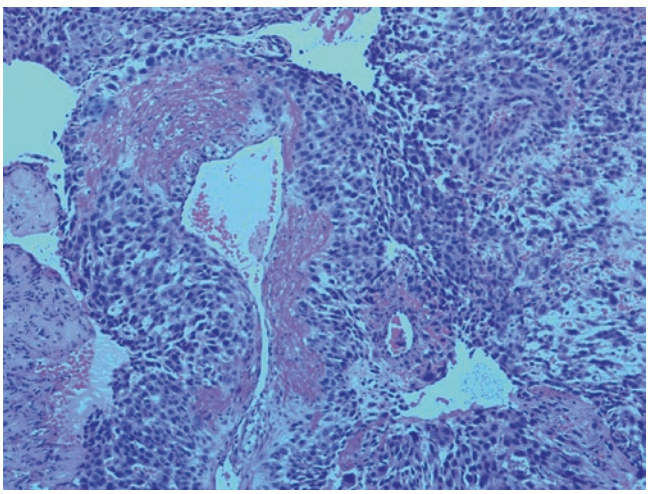

Fig. 13.36 Conspicuous perivascular growth with fibrin deposit in PSTT

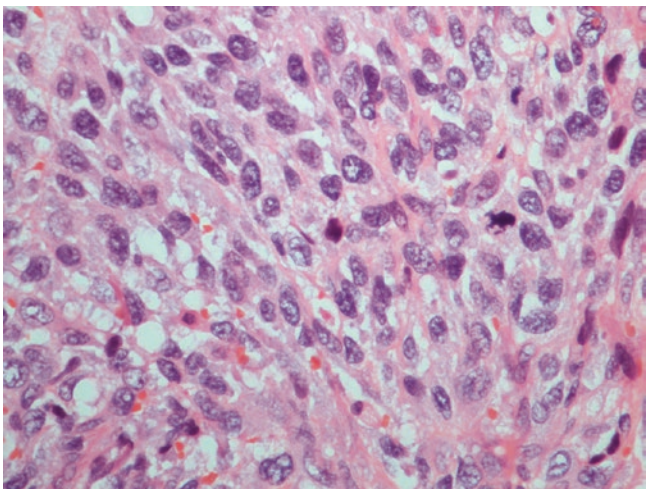

Fig. 13.37 Solid aggregates of PSTT tumor cells with nuclear pleomorphism and brisk mitotic figures

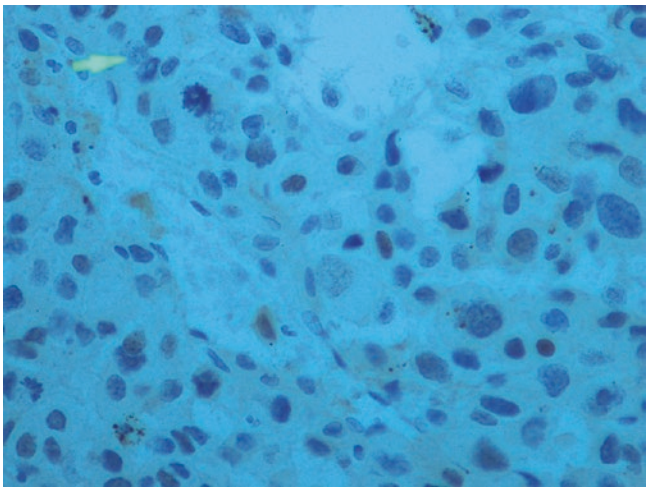

Fig. 13.39 The tumor cells of PSTT are often negative for p63 and may be helpful to distinguish from poorly differentiated non-keratinizing carcinoma in a cervical biopsy

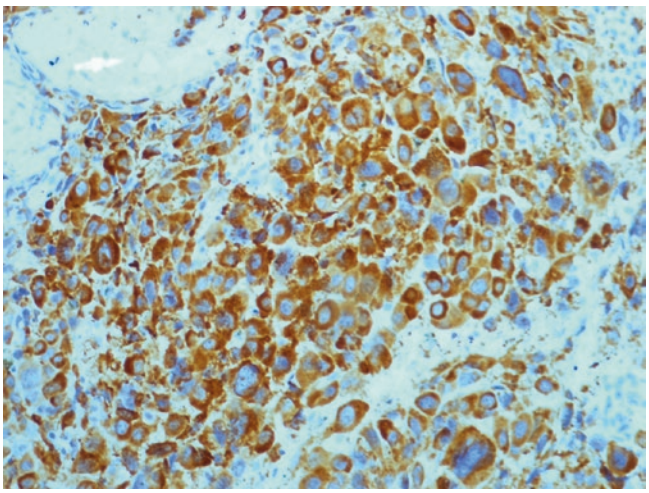

Fig. 13.38 The cytoplasm of PSTT tumor cells is positive for hPL

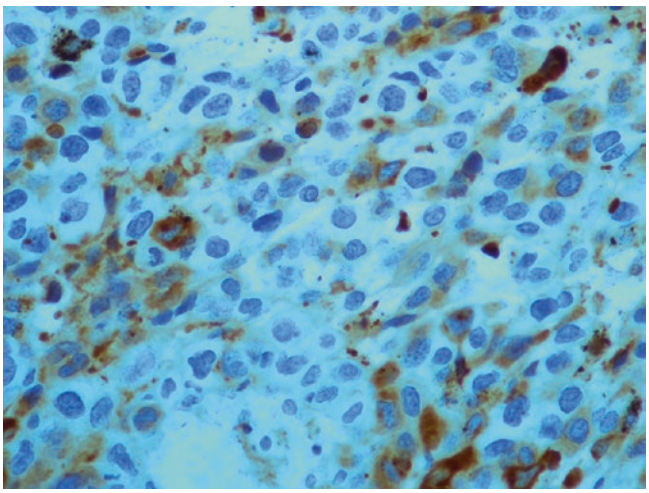

Fig. 13.40 Focal immunoreactivity for hCG can be demonstrated in PSTT

13.8.4 Biomarkers

The tumor cells are positive for cytokeratins, hPL (Fig. 13.38), CD10, inhibin, Mel-CAM (CD146), and HLA-G. It is often negative for p63 (Fig. 13.39). The hCG staining is usually limited to the multinucleated cells (Fig. 13.40). The MIB1 proliferative index (ki-67) is usually >10% [10, 120, 139].

13.8.5 Genetic Profile

There is usually a paternal X chromosome. There are occasional cases which show genetic imbalances [124, 140–143].

13.8.6 Differential Diagnoses

The differential diagnoses include choriocarcinoma, epithelioid leiomyosarcoma, poorly differentiated carcinomas, melanomas, and exaggerated placental site reaction [25] (Tables 13.4 and 13.6).

Unlike placental site trophoblastic tumor, choriocarcinoma usually has a combination of features including very high serum hCG, a hemorrhagic mass, and a plexiform growth but lacking the angiocentric and angioinvasive pattern of placental site trophoblastic tumor (see under differential diagnosis of choriocarcinoma). Poorly differentiated placental site trophoblastic tumor may be indistinguishable from some choriocarcinomas and may rarely coexist.

Table 13.6 Differentiated diagnosis of PSTT

	PSTT	CCA	Epithelioid leiomyosarcoma	Poorly differentiated carcinomas
Serum hCG level	Mildly elevated	Markedly elevated	Normal	Normal
Histological feature	Angiocentric-angioinvasive pattern	Hemorrhagic mass with plexiform growth	Arranged in sheets, nests, cords that may form a plexiform pattern	Arranged in sheets, nests, cords
Tumor cell origin	IT	CT, ST, villous IT	Smooth muscle cell	Epithelial cell
Fibrinous deposition	+	–	–	–
hCG immunostain	+	+++	–	–
Pan-cytokeratin	+	+	–	+
Muscle marker	–	–	+	–

PSTT placental site trophoblastic tumor, *CCA* choriocarcinoma, *IT* intermediate trophoblasts, *CT* cytotrophoblasts, *ST* syncytiotrophoblasts

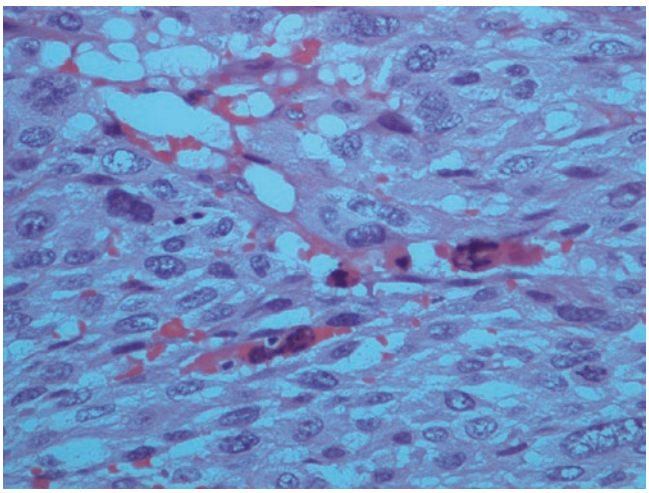

Fig. 13.41 Spindle-shaped PSTT cells with eosinophilc degeneration resemble keratinizing squamous cell carcinoma of cervix

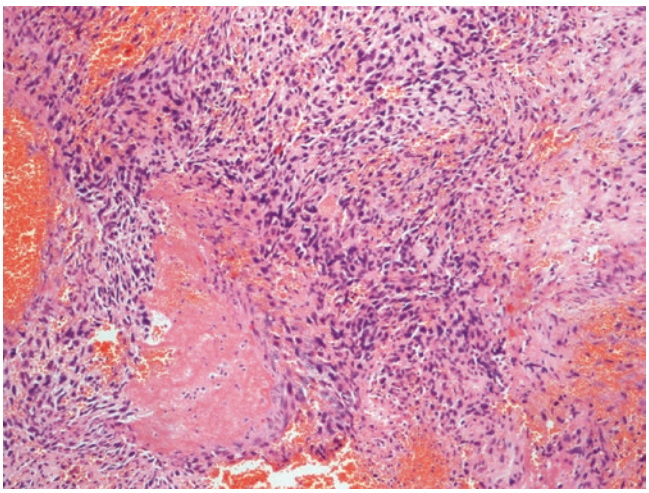

Fig. 13.42 Spindle-shaped PSTT cells resembling leiomyosarcoma

Distinction from epithelioid leiomyosarcoma, poorly differentiated carcinomas, and melanomas in the uterine corpus or cervix may be difficult particularly during interpretation of frozen section or small biopsies (Figs. 13.41 and 13.42). Identification of more typical histopathological features and immunohistochemical profiling are helpful in the differential diagnoses. PSTT usually shows permeation of blood vessel wall, splitting apart of well-preserved myometrial cells, and conspicuous fibrinoid deposit. Epithelioid leiomyosarcomas may be confirmed by absence of the distinctive vascular pattern of placental site trophoblastic tumor; immunoreactivity for h-caldesmon, desmin, and actin; and negative for hPL and inhibin. Poorly differentiated carcinomas usually show some histologic evidence of a better differentiated component (squamous or glandular) and an immunoprofile of hPL/hCG/inhibin nonreactivity.

13.8.7 Prognosis and Outcome

The majority of patients present at FIGO stage I [132]. Approximately 30% are high stage with involvement of other pelvic sites, and metastases to lymph nodes, lungs, and liver. Half of these patients may die from tumor. Metastases and recurrent tumors respond poorly to chemotherapy and often result in fatality. Pathologic features associated with poor outcome include extensive necrosis, cells with clear cytoplasm, deep myometrial invasion, and >5 mitotic figures per 10 high-power fields. In multivariate analysis, FIGO stage III/IV, a latency of ≥2 years since last pregnancy, and presence of clear cells are independently associated with a poor prognosis [133, 144–147].

13.9 Epithelioid Trophoblastic Tumor

13.9.1 Definition

Epithelioid trophoblastic tumor is a malignant trophoblastic tumor of intermediate trophoblasts. The cell of origin is believed to be chorionic-type trophoblasts [148].

13.9.2 Clinical Features

The affected women are usually in the similar age group as placental site trophoblastic tumors (with a mean age of 36 years) and commonest presentation is abnormal vaginal bleeding and a mildly elevated serum hCG. In addition to the corpus, 50% of tumor commonly arises in the lower uterine segment and cervix and often have a long interval from an antecedent pregnancy (with a mean of 6 years), which may be a term pregnancy, abortion, or hydatidiform mole [148–152].

13.9.3 Pathological Findings

Grossly, the tumor may be nodular infiltrative masses but often with involvement of mucosa associated with ulceration [148, 153]. The cut surface may show necrosis and hemorrhage. Microscopically, the tumor cells are arranged in expansile nodules, nests, or cords separated by abundant extracellular eosinophilic hyaline-like material (Fig. 13.43) [148, 151, 154]. Geographic necrosis and perivascular viable tumor cells are often striking. In some cases, decidualized stromal cells may be found at the periphery. The tumor cells are mononuclear, well-defined cell membrane, uniform in size with eosinophilic or clear cytoplasm. There is moderate nuclear atypia and a low mitotic count (range between 0 and 10 mitotic figures per 10 high-power fields, with a mean of 2) [139].

13.9.4 Biomarkers

There is immunoreactivity for H3D3B1, CD10, and cyclin E but also cytokeratins, EMA, and p63 (Fig. 13.44). Staining for other trophoblastic markers, such as hPL, hCG, inhibin, Mel-CAM, and HLA-G, may be focal. The MIB1 proliferative index (ki-67) ranges from 10% to 25% [10, 12, 120, 155, 156].

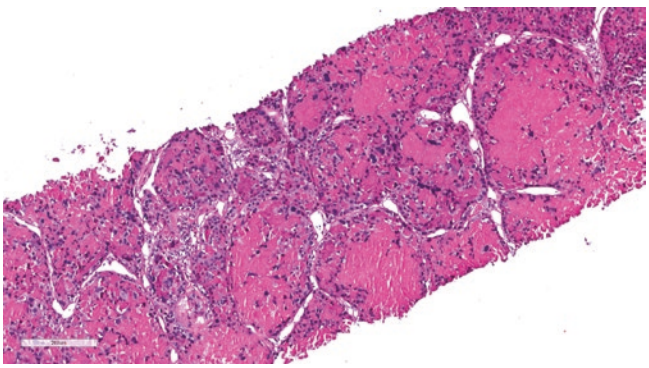

Fig. 13.43 A metastatic ETT presented as lung nodule. Cellular nodules and nests are separated by abundant extracellular eosinophilic material

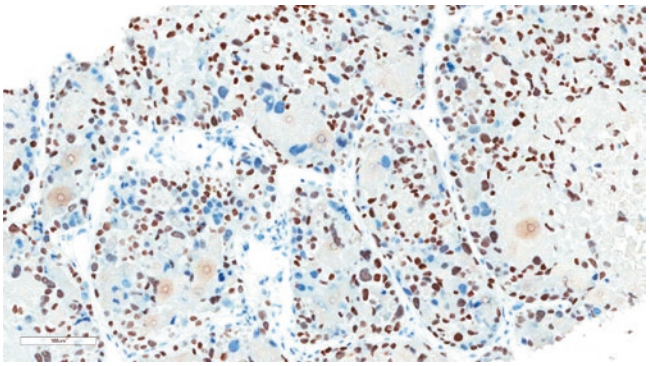

Fig. 13.44 The ETT cells are positive for p63

13.9.5 Genetic Profile

The majority lack Y chromosome complement [124]. Rare comparative genomic hybridization studies showed an undisturbed genome [140, 157]. There are some suggestions of malignant transformation from a preexisting placental site nodule [158].

13.9.6 Differential Diagnosis

These include squamous cell carcinoma, epithelioid leiomyosarcoma, and other gestational trophoblastic tumors [25] (Table 13.4). In small biopsies, distinction from placental site nodule may be difficult.

Some of the gross (cervical mucosal involvement) and microscopic features (epithelial involvement resembling high-grade squamous intraepithelial lesion, eosinophilic hyaline material) and immunoprofile (positive staining for cytokeratins, EMA, and p63) of epithelioid trophoblastic tumors mimic those of squamous cell carcinomas. Overt squamous differentiation, absence of staining with trophoblastic markers, and a normal serum hCG level support squamous cell carcinoma [151, 159, 160].

Epithelioid leiomyosarcoma usually contains a component of more typical smooth muscle tumor differentiation and is immunoreactive for smooth muscle markers. Compared with epithelioid trophoblastic tumor, placental site trophoblastic tumor has a more infiltrative dissecting growth, has a typical angiocentric and angioinvasive pattern, and shows more extensive staining with hPL and Mel-CAM and negative for p63. Epithelioid trophoblastic tumors may coexist with other gestational trophoblastic tumors as mixed tumors. Some choriocarcinomas which have been treated with chemotherapy may show degenerative features which

are difficult to distinguish from some epithelioid trophoblastic tumors [161].

Placental site nodules are hypocellular and diffusely hyalinized, and the cells are mitotically inactive, negative for cyclin E. The MIB1 proliferative index is <5%. Atypical placental site nodule is a term applied to indeterminate lesions when the spectrum of features between a nodule and an epithelioid trophoblastic tumor is unclear [155, 158].

13.9.7 Prognosis and Outcome

The only histologic feature associated with a poor outcome is a high mitotic count >6 per 10 high-power fields. Patients without metastases have excellent prognosis. In 25% of patients, there is blood-borne metastasis and half of these usually died of tumor [151, 162].

13.10 Exaggerated Placental Site

13.10.1 Definition

Exaggerated placental site is the unusual prominence of implantation-site intermediate trophoblasts found at the implantation site of a placenta (synonym: exaggerated placental site reaction) [139, 163].

13.10.2 Pathological Findings

Exaggerated placental site may be seen in first-trimester induced or spontaneous abortions and has been suggested to be more common in association with an underlying hydatidiform mole (Fig. 13.45) [163]. There is usually no gross lesion. The distinction between what constitutes a normal or exaggerated placental site is unclear and subjective. In a definitive case of exaggerated placental site, there is a striking increase in the number of intermediate trophoblasts in the endometrium and myometrium, either in small nests, sheets, or individually, and without destructive invasion of the myometrium such that the myometrial anatomy is preserved. These cells are recognized under low-power magnification due to the nuclear atypia, hyperchromasia, and multinucleation [164]. They are usually mitotically inactive [13, 139].

13.10.3 Biomarkers

The intermediate trophoblasts are immunoreactive for cytokeratins, hPL, inhibin, Mel-CAM (CD146), and MIB1 proliferative index (ki-67) <1% [122, 123, 165].

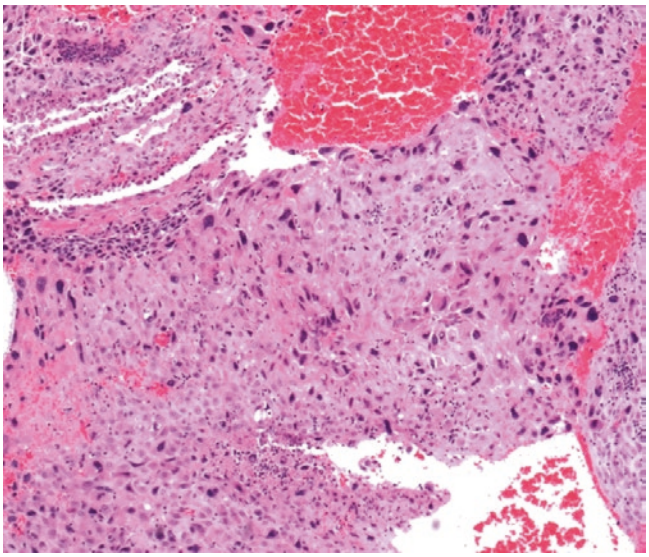

Fig. 13.45 Photomicrograph of exaggerated placental site reaction found with complete mole

13.10.4 Differential Diagnosis

Placental site trophoblastic tumor is favored in the presence of a mass (clinically or radiologically), high serum hCG levels, destructive myoinvasion, typical angioinvasive pattern, tumor necrosis, and a MIB1 proliferative index >10%. A low MIB1 index and presence of decidua and villi are in favor of exaggerated placental site.

13.10.5 Prognosis and Outcome

Exaggerated placental site usually regresses spontaneously. There is no proven genetic relationship with placental site trophoblastic tumor. The consistent XX genome of PSTT is not seen in cases of exaggerated placenta site [140, 166].

13.11 Placental Site Nodules/Plaques

13.11.1 Definition

These are circumscribed nodules or plaques composed of chorionic-type intermediate trophoblasts within an abundantly hyalinized stroma [139, 167–169].

13.11.2 Pathological Findings

Nodules or plaques are usually discovered in hysterectomy or uterine curettage specimens when the patient is undergoing investigations for other gynecological conditions, such as

abnormal menstrual bleeding. Patients are usually in their reproductive years and had an antecedent pregnancy dating back to 8 years (with a mean of 3 years). Rarely, the presentation is of someone being investigated for postmenopausal bleeding. The usual sites of involvement are lower segment endometrium, and endocervix [167]. Only 25% of lesions are grossly visible as tan to brown solid nodules. Microscopically, the lesion is hypocellular and has abundant eosinophilic hyalinized stroma in which individual and clusters of cells are seen (Fig. 13.46). The cells have variable amount of eosinophilic to clear cytoplasm, and irregular and pleomorphic nuclei with smudged nuclear chromatin. Mitotic figures are typically absent. Some cells may contain cytoplasmic eosinophilic hyaline material. Fibrinoid necrosis and dystrophic calcification are common. Rarely, necrotic or degenerated chorionic villi with ghost outline are also seen [168].

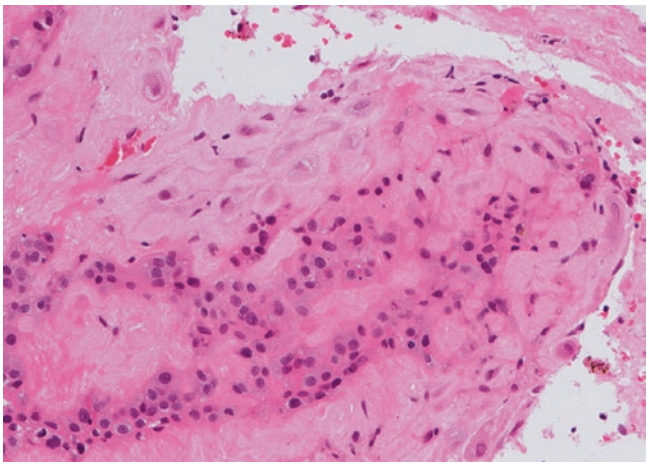

Fig. 13.46 Hypocellular nodule of PSN with conspicuous eosinophilic hyalinized stroma is detected incidentally in a uterine curetting

13.11.3 Biomarkers

The cells are immunoreactive for cytokeratins, EMA, CD10, p63, and inhibin (Fig. 13.47). Implantation-site trophoblast markers such as hPL and Mel-CAM are less often positive. The MIB1 proliferative index (ki-67) is <8%. Unlike epithelioid trophoblastic tumors, nodules are negative for cyclin E [11, 13, 123, 155, 170].

13.11.4 Differential Diagnosis

Decidual reaction may mimic placental site nodules. The decidualized stromal cells are usually more uniform in size and shape and lack nuclear hyperchromasia. They do not express the immunomarkers of a placenta-site nodule. Exaggerated placental site is less often hyalinized and less well circumscribed.

Unlike placental site nodule, the cells in placental site trophoblastic tumor are implantation-site intermediate trophoblasts and immunophenotypically different. A placental site

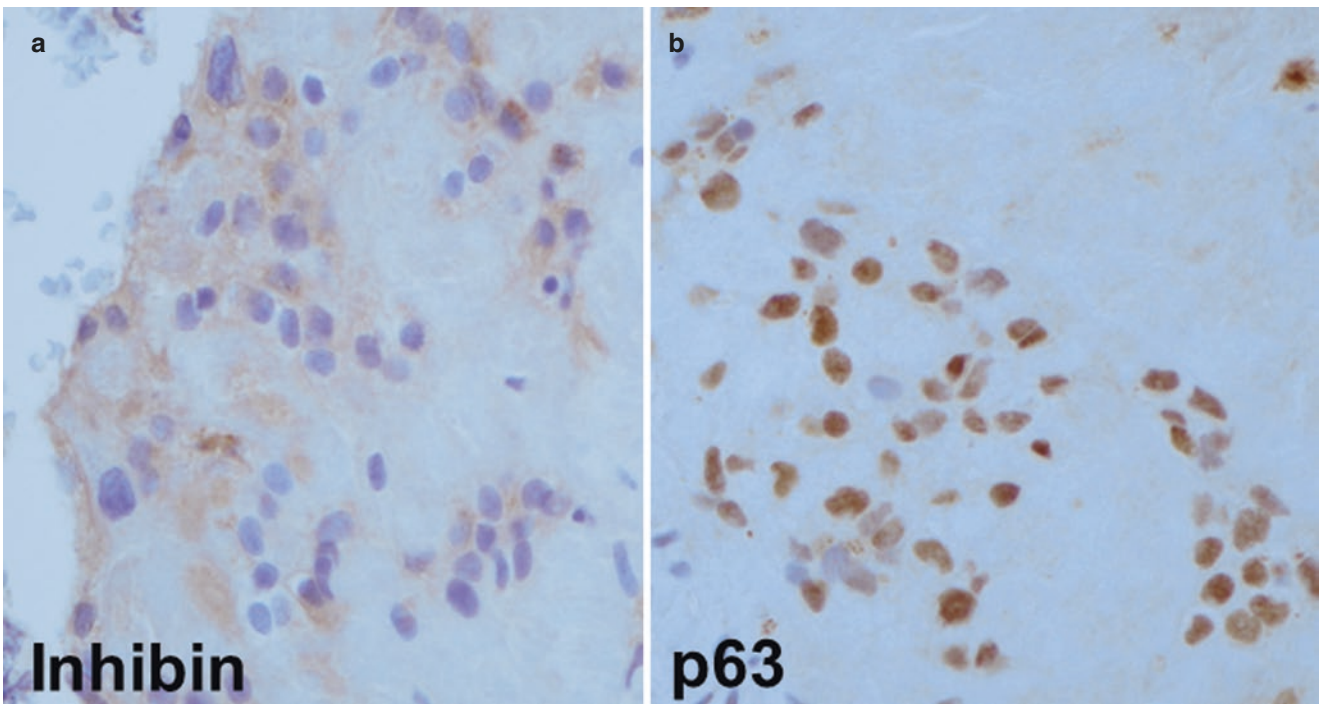

Fig. 13.47 The chorionic intermediate trophoblasts at this PSN are negative for inhibin (**a**) but positive for p63 (**b**)

trophoblastic tumor is often a large infiltrative mass with high MIB1 index.

Distinction of a placental site nodule from epithelioid trophoblastic tumor, which bears the same type of intermediate trophoblasts, may be difficult especially in curettage samples. A nodule usually has a lower cellularity, more diffusely hyalinized, and the cells are nonimmunoreactive for cyclin E, and have a MIB1 index of <8%. In cases in which the distinction between a nodule and a tumor cannot be made with certainty (in which cases the nodules are larger than usual, focally infiltrative border, increased cellularity, moderate nuclear atypia, presence of mitotic figures, and MIB1 index of 8–10%), it has been suggested that the term "atypical placental site nodule" may be used [155, 158].

Other differential diagnoses of placental site nodule include squamous cell carcinoma and epithelioid smooth muscle tumors and are discussed under epithelioid trophoblastic tumor.

13.11.5 Prognosis and Outcome

These are benign lesions and follow-up on these patients has been uneventful. Lesions considered atypical placental site nodules are suggested to be premalignant to epithelioid trophoblastic tumors [158, 171]. Patients with atypical placental site nodule should be evaluated by imaging studies to exclude the presence of a mass lesion, and should be under close surveillance with serial hCG measurements.

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