EXTRAGENITAL CHORIONEPITHELIOMA IN THE MALE

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Chorionepithelioma was described by Sänger (1) as long ago as 1889. He called attention to the symptoms and diagnosis of this tumor, believing it sarcomatous in nature, and interpreted its origin as from the maternal decidua. In 1895 Marchand (2) first suggested that the Langhans cells were fetal in origin—the syncytial cells the maternal contribution. As a result of subsequent study (3), however, he was able to trace all cellular components from the trophoblast. In 1910 Ewing (4) gave us to understand that microscopic findings in these tumors were difficult to associate with the factor of growth capacity.

The majority of investigators are impressed with the attendant difficulties in arriving at a clinical and pathological diagnosis. A complicating factor is that normally the trophoblast is an invasive tissue, and in this respect resembles cancer. In normal pregnancy chorionic villi may be found in the walls of the uterus, particularly in the veins, and, according to Schmorl (5), are often transported to the lungs. A still more perplexing fact is that chorionepitheliomatous tumors comprise diverse forms, which vary considerably in their clinical features.

Malignant chorionepithelioma, though its very name implies a placental origin, is nevertheless a tumor occurring in both sexes. In the male, chorionepitheliomatous structures have long been described and studied, and various theories as to their origin have been set forth. In 1878 Malassez and Monod (6), and later Carnot and Marie (7), described a series of growths of the testicle resembling hydatid mole. They noted especially the multinucleated giant-cell masses which were in relation to the blood vessels and designated the tumor sarcome angioplastique. Schlagenhaufer (8) in 1902 called attention to a resemblance between this type of tumor in males and the chorionepithelioma of trophoblastic origin. He was the first to suggest that the two were identical, and his contention is unquestioned today. That the resemblance is more than superficial is shown, in the first place, by the fact that in these cases the male breast may assume a physiological activity which is comparable to that of the female type. Cases in which gynecomastia is one of the outstanding features have been reported by
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Warthin (9), Cooke (10), and Herzenberg (11). In the second place, hypophyseal hormone has been found by Aschheim and Zondek (12) in the urine of men known to have chorionepithelioma, so that the urine gives a positive reaction to the Aschheim-Zondek test as does the urine in normal pregnancy. Since the clue was first given by Schlagenaufier, many others have collected and reported cases of chorionepithelioma in the male. D'Arcy Prendergast (13), in April 1929, collected a total of 118 cases. This number may now be raised to at least 131.

With few exceptions, chorionepithelioma in males occurs primarily in the testicle. The prognosis is almost invariably grave. Deaths from chorionepithelioma within two months of the onset of symptoms are recorded, but survivals for periods in excess of two years are also reported.

Theories concerning the origin of testicular chorionepithelioma are numerous. Often in the original tumors and occasionally in metastatic growths, teratogenous elements have been found. This has led some investigators to use the theories of origin of the teratoma in an effort to explain the genesis of chorionepithelioma. This point has recently been re-emphasized by Hörmicke (14), who believes that teratogenous elements are often overlooked. The question is, of course, unsettled. The French by the very title sarcome angioplastique expressed their advocacy of an endothelial origin. An epithelial genesis is upheld by many. The incidence of chorionepithelioma in the testicle within the years of spermatogenic activity has given rise to a theory of increasing popularity, i.e. an origin from totipotential cells. Trauma to the testicles, including the undescended testicle, has been a definitely associated factor in not a few cases. The hypothesis of misplaced blastomeres with subsequent malignant degeneration has appealed to many as a possible explanation. The studies of Schmorl, concerning hematogenous dissemination of chorionic elements during pregnancy, have interested Tansey and Utz (15), who see no reason why chorionic wandering cells should not enter into the fetus as well as into the body of the mother, and there give rise to chorionepitheliomatous growths. The work of Hansmann and Budd (16) on unattached retroperitoneal tumors, chorionepithelioma in the male included, has revived the concept that extratesticular chorionepithelioma may originate from remnants of the embryonal urogenital apparatus.

In recent years, there has been much discussion concerning the question of primary extragenital chorionepithelioma in the male. Oberndorfer, as quoted by Kantrowitz (17), writes: "dass beim Mann das Chorionepitheliom immer mit Keimdrüsengeschwülsten in Zusammenhang stehen muss." Prym (18), reviewing the litera-
ture of alleged cases, accepts only that of James Ritchie, which is "an account of a case where a dermoid cyst occurred in the anterior mediastinum, and where there was associated with this common tumor a malignant growth of very unusual characters." Prym is opposed to regarding other reported cases as primary extragenital chorionepithelioma. Ewing (19) suggests that these tumors are probably primary carcinoma, simulating chorionepithelioma, or metastatic chorionepithelioma from the testicle, the primary tumor having been overlooked. However, cases which appear to be asexual or primary extragenital chorionepithelioma, continue to be reported from time to time. Some of the most conclusive reports, oddly enough, appear in the literature written in English. Summaries of these cases follow, with an additional report of a case of undetermined origin observed in this laboratory.

**CASE I, REPORTED BY JAMES RITCHIE (20):** A young man aged twenty-four complained of pains in the right mammary region, with cough and general malaise for three days. The pulse rate was 116, respirations 36 per minute, temperature 101° F. On examining the chest it was observed that the right side seemed to expand less freely than the left; on percussion the note was resonant over the chest, back and front, except for a circular area extending from the lower margin of the first left rib down to the site of normal cardiac dullness, and from the right margin of the sternum to a point about two inches to the left of the sternum. Inquiries disclosed the fact that the illness was of longer duration than stated by the patient. He had been observed to be in poor health and less active than formerly for a period of about three months; for six weeks he had every morning expectorated a quantity of bright red blood. Constant and distressing cough was present, and at frequent intervals there was a return of the hemoptysis. About a week after the patient was first seen, dyspnea became acute. He became markedly weaker and died.

**Neeropsy:** Post-mortem examination revealed a dermoid cyst of the anterior mediastinum. Attached to and forming part of the wall of this cyst was a solid growth of a malignant nature, composed largely of necrotic tissue but containing areas of living cells. These cells were microscopically of three main types: (a) closely packed polyhedral cells, with both nucleus and cytoplasm much vacuolated; (b) enormous protoplasmic sheets, multinucleate and with intensely staining cytoplasm; (c) small cells, in smaller numbers than the other two types, whose staining reactions conformed closely with those of the second group. Irregularly interspaced between these cell masses were large areas of hemorrhage, with numerous red blood corpuscles, partly apparently normal, often showing evidence of breaking down, and many large phagocytes containing their remains.

Both lungs were riddled with metastases varying in size, the largest being about 5 cm. in diameter. There were several similar tumors in the liver, and one about 2 cm. in diameter in the spleen. These secondary growths had the same gross appearance as the solid part of the primary tumor and likewise contained numerous hemorrhagic areas.

There was no abnormality in the testicles.

**CASE II, REPORTED BY VICTOR BONNEY (21):** A boot-maker aged sixty-nine had been in good health all his life until he noticed a slight swelling of his ankles eight weeks prior to his admission to the German Hospital, Dalston. The swelling increased and extended upwards; later the abdomen became enlarged. There was loss of weight and appetite.
On admission the patient was thin, the lower extremities showed marked edema, and there was ascites with distention of the superficial abdominal veins. In the mid-line of the abdomen, between the symphysis pubis and the umbilicus, was a hard mass, somewhat ill-defined on account of the ascites. The mass was not painful on pressure, but the patient complained of a sensation of distress. Nine days after admission the abdomen was tapped and 4000 c.c. of a serosanguineous fluid was withdrawn. In spite of the relief the patient subsequently died.

Necropsy: Immediately beneath the anterior abdominal wall, apparently situated in the great omentum, was a lobulated tumor the size of a man's head, of a deep red color, and soft in consistency. On section it was solid throughout and presented a number of hemorrhagic areas. The liver was enlarged and lobulated and contained a number of metastases which showed great variation in size. Both testicles appeared normal. No other metastases were found.

Microscopically the cellular elements of this tumor were of three distinct types. (a) Immediately under the capsule was a tract of small hyaline cells, massed together, and exhibiting a vesicular nucleus. (b) Large irregular syncytia of variable shape bounded the hyaline cell masses and extended out to the capsule in irregular fashion. The nuclei varied greatly, being lobulated, pale and vacuolated in some areas and elongated, flattened and deeply chromatic in others. (c) There were also irregular cells exhibiting all gradations in size and shape between the hyaline cells and the syncytia. These varied, some being vesiculated, deeply chromatic or vacuolated, with round, oval, or lobulated nuclei. Not infrequently giant nuclei were observed, especially in the more central portion of the mass. The metastases in the liver presented the same features microscopically as the areas examined in the main tumor mass. There were no elements found which suggested a teratogenous origin.

Case III, reported by Parkes Weber (22): A strongly built man aged twenty-three years was admitted to the Military Hospital at Bedford with a history of hemoptysis. Until four days prior to admission he had been quite well. Four days later he was transferred to the Bedford County Hospital with signs of intraperitoneal hemorrhage, and with the additional complaints of hematemesis, melena, and hematuria. Exploratory laparotomy disclosed arterial bleeding from a rupture on the under surface of the liver. This was packed, but the patient died an hour later.

Necropsy: The liver was enlarged, and on its anterior, inferior, and posterior surfaces were irregular nodular, hemorrhagic, purplish areas of growth averaging about 3 or 4 cm. in diameter. Immediately below and to the left of the bifurcation of the aorta was a large retroperitoneal mass, which had the same purplish, hemorrhagic appearance as the growth of the liver. In the lungs, near the surface, were multiple circumscribed areas of growth, purplish and hemorrhagic like those of the liver. There were no other metastases and no abnormalities about the testicles.

Microscopically the sections showed large spaces or sinuses which contained blood and clot and showed the following types of cells: (a) cubical or polygonal cells lining the sinuses and forming blocks or clumps in areas adjacent to the sinuses; (b) large protoplasmic sheets projecting into the sinuses in some areas and in others lining the sinuses in the place of the polygonal-cell masses; (c) giant-cell masses closely surrounding the polyhedral cells, which, like the syncytium, projected into the sinuses.

Case IV, reported by Miller and Browne (23): A cattle-man aged thirty-nine years was admitted to the Edinburgh Royal Infirmary complaining of an intermittent pain in the lower part of the chest on the right side, of six weeks' duration. The pain had been slight at first, but had become increasingly severe. It was only after admission to the Infirmary that the patient noticed any swelling of
the abdomen. He was poorly nourished and complained of loss of appetite. The pain became more constant and of a severe stabbing nature. The liver was markedly enlarged, the abdominal swelling increased, and the patient became jaundiced. Large quantities of fluid were drawn off at intervals. Death occurred thirty days after admission.

Necropsy: The abdominal cavity was filled with fluid and clotted blood. There was a slight excess of fluid in both pleural cavities. The left lung was edematous, the right partially collapsed. The liver was enormously enlarged and showed several tumor-like masses beneath the capsule. Immediately behind the liver was a large mass enclosed in a fibrous capsule. Several of the retroperitoneal lymph nodes were infiltrated with tumor tissue.

Microscopically the tumor presented the following features: (a) small masses of protoplasmic syncytium of irregular outline containing numerous nuclei and in some places presenting a foamy or alveolar appearance; (b) large numbers of polyhedral cells mixed indiscriminately with the syncytial masses, occurring singly or in groups, forming a more or less perfect mosaic pavement and varying widely in size, shape, and appearance; (c) areas in which the cells differed from the other two types in that they lay in closely packed masses, with a hyaline protoplasm. In the sections there was a cyst containing hemorrhagic, fibrinous, and necrotic material with many thin-walled blood vessels. There were smaller spaces almost invariably lined by syncytium which was in some places necrotic. Sections of the liver showed the three cell types found in the main tumor mass. The testicles were normal.

CASE V, REPORTED BY P. V. KRAVJANSKAIA (24): A man aged seventy-two years complained of shortness of breath and stabbing pains in the heart, which were referred to the left arm.

Necropsy: The peritoneal surfaces presented numerous pin-point hemorrhages. There was a large mass at the hilus of the left lung, extending out into the mediastinum. This mass the author considers as primary. There were numerous smaller nodules in the brain, liver, spleen, pancreas, kidneys, retroperitoneal lymph nodes, and lungs.

Microscopically the primary tumor of the left lung showed large areas of hemorrhage, fibrin masses, and regions of necrosis. The cellular elements were as follows: (a) Syncytial masses with fragmented and pyknotic nuclei ramified in all directions and extended into or surrounded the blood sinuses. In some areas the staining reaction was normal, in others the nuclei appeared vacuolated. (b) Polyhedral cells of the Langhans type, with round or ovoid nuclei and a clear protoplasm, were distributed chiefly around the periphery of the tumor, in which regions there was a marked dilation of blood vessels. Serially sections of the testicles showed no histologic changes.

CASE VI, REPORTED BY A. R. KANTROWITZ (17): Necropsy of a man aged twenty-two disclosed a teratoma of the anterior mediastinum containing chorion-epitheliomatous elements. The tumor invaded the superior vena cava and both lungs were studded with chorionepitheliomatous metastases. No other metastases were found. The genital tract showed no tumor nodules. The testicles were cut in 2 mm. blocks, and sections from each block revealed no tumor nodules, but interstitial-cell hyperplasia was seen. Microscopic examination of the main tumor mass revealed teratomatous and chorionepitheliomatous elements. The Aschheim-Zondek test was positive both in the urine and in the extracts of the tumor tissue.

CASE VII, REPORTED BY LAMBERT AND KNOX (25): A man aged thirty-seven complained of pain in the left chest of one month's duration.

Necropsy: The left pleural cavity contained one liter of straw-colored fluid. The upper part of the mediastinum was occupied by a mass as large as a cocoanut. The right lung was edematous and showed numerous elevated nodules. The left
lung was atelectatic and its surface was studded with similar nodules. The left parietal pleura showed elevated, reddish nodules. There were also nodules of hemorrhagic tissue in the liver.

Microscopically the tumor contained elements of skin, intestine, the central nervous system, muscle, bone, cartilage, and teeth. There were areas of typical chorionepithelioma, the structure of which was duplicated in the metastases in the lungs, pleura, and liver.

Case VIII, Author's Case: A man forty years of age entered the Illinois Central Hospital. Four weeks before admission he complained of backache, and a week later he began to lose weight, having lost about forty pounds since. Two weeks before admission his present complaint began with vomiting, anorexia, pain, and tenderness in the epigastrium. His stomach had not troubled him in the least up to that time, but since then food was not retained at all. The pain was constant and dull but could not be referred anywhere. The vomiting had no effect on the pain and was very distressing. A blood count showed 6,000,000 red and 11,400 white cells. The differential count was normal. There was some albumin in the urine.

Physical examination showed simply a rapidly growing tumor mass in the epigastrium; the x-ray showed a shadow at the pylorus and complete retention of the test meal for nine hours when not vomited. Exploratory operation on the second day after admission revealed a large retroperitoneal tumor mass pushing forward the stomach and the pancreas, but with no signs of infiltration. A piece of tissue was removed and the histologic diagnosis was "polymorphic-cell sarcoma." At the request of the patient, and as a last resort, a second operation was performed five days after the first. This attempt to remove the mass was unsuccessful, and death occurred immediately after the operation, from shock.

Necropsy: The post-mortem examination was made immediately after death by Dr. H. G. Wells. The anatomical diagnosis was as follows: primary retroperitoneal chorionepithelioma probably derived from the urogenital anlage, distending the inferior vena cava and the left renal vein; metastasis to the lungs; atrophy of the right testicle.

The autopsy findings of interest are as follows:

Abdominal Cavity: Over the pylorus are two white nodules, one 2 cm. in diameter, the other pin-point in size. The only adhesions are a few fresh ones about the gallbladder. There is some laceration in the posterior peritoneal wall over a retroperitoneal mass, with some fresh blood clots.

Thoracic Cavity: The right lung is normal but in the left lung are two hyperemic areas 1 cm. in diameter each containing a small whitish central nodule 3 mm. in diameter. The mediastinal lymph nodes are not palpably enlarged. In the fat of the upper surface of the diaphragm on the right side is a pinkish nodule, apparently a lymph node. The pericardial cavity and heart are normal.

Gastro-Intestinal Tract: The stomach is not adherent or involved in the tumor. About 2 cm. above the ampulla of Vater is a white submucous nodule about 3 cm. in diameter. There are no other abnormalities.

Kidneys: The right kidney has been stripped of its capsule, otherwise appearing normal, although there is some submucous hemorrhage in its pelvis. The right renal vein does not contain any tumor thrombi. The left kidney is likewise normal. The left renal vein is nearly surrounded by the tumor mass, while near the vena cava there is a 2 mm. tumor nodule in its wall protruding slightly through the intima. The tumor does not invade or adhere to the other kidney.

Generative Organs: The prostate, seminal vesicles, epididymis and left testicle are normal. The right testicle is half the normal size, but shows no tumor growth or other abnormality.

Skeleton: There are no nodules or attachments of the tumor to any part of the
vertebral column, although the tumor has infiltrated to the periosteum. There are no palpable metastases in any part of the skeleton.

Tumor: In the mid-line, directly behind the head of the pancreas but not involving it, is an irregular rounded tumor mass, with a nodular surface covered with peritoneum, the left border being slightly to the left of the left margin of the vertebral column and the right three fingers' breadth to the right of the vertebral column, passing towards the hilum of the right kidney. The entire mass measures 11.5 x 10.4 x 8 cm.

The tumor causes a bulging of the intima of the inferior vena cava just below the renal veins for a distance of 5 cm., and in very small areas it has penetrated the intima. The vena cava is crowded to the right and forward by the tumor, at the base of which it lies. The mass is freely movable on its anterior portion. It has surrounded and slightly flattened the abdominal aorta below the renal veins but has not invaded it. The tumor tissue is about the consistency of liver tissue, very friable, and extremely rich in blood. Posteriorly it reaches to the fascia covering the vertebrae, but in no place invades or erodes the bone. The point of origin of the tumor cannot be determined. It does not arise from any of the retroperitoneal organs. It does not involve the adrenals or kidneys.

**Histological Report:** The primary tumor resembles exactly a choriocarcinoma, with typical arrangement of large protoplasmic sheets of multinucleated cell masses representing the syncytiun, interspaced by the cuboidal or polyhedral cell groups representing the Langhans type (Fig. 1). Irregularly distributed between these areas is considerable necrosis, and hemorrhage is nearly everywhere present. There are many mitoses in both types of cells. No teratomatous elements are present. The secondary encapsulated metastatic tumor in the lung is similar in every respect to the primary tumor. There is compensatory local emphysema in the lung tissues around the metastasis.

In the right testicle the cells of Leydig are grouped into conspicuous islands; there are new hemorrhage and a deposition of blood pigment and fibrin, probably the result of an old trauma. No evidence of tumor tissue is found.

Attached to the duodenum is an accessory pancreas and Brunner's glands are dilated. No metastatic growths were found except in the lungs, and the other organs showed no changes of importance.

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**FIG. 1.** **CHORIONEPITHELIOMA ARISING IN RETROPERITONEAL TISSUES OF THE MALE:** TYPICAL CHORIONEPITHELIOMA STRUCTURE WITH MASSES OF SYNCYTIAL CELLS AND AREAS OF LANGHANS' CELL TYPE. × 125
Comment

This case is apparently quite typical of chorionepithelioma. The sudden onset of symptoms, becoming increasingly severe, together with rapid loss of weight, unlocalized pain, and diminishing vitality correspond to the usual history in such cases. The finding of a hemorrhagic, necrotic mass in the retroperitoneal area, with pulmonary metastasis of a similar nature, the histology of which reveals syncytial cell masses and polyhedral cells representative of the Langhans type in the normal placenta, seems sufficient to justify the interpretation.

Theories concerning histogenesis are extremely varied. As in the cases cited from the literature, origin from the developed generative organs can be excluded. The fact that the atrophic right testicle shows microscopically old and recent hemorrhage, together with a scarred area, suggestive of trauma, is not sufficient evidence to warrant interpretation of a testicular origin, since microscopic examination revealed no tumor tissue. Absence of involvement of the lymph nodes is also against the possibility that the retroperitoneal tumor could have been merely a metastatic growth from a primary testicular tumor which had in some mysterious manner disappeared leaving no traces beyond a scar. Injury to the testicle, as has been mentioned, is a very definite associated factor in some cases, but with the injury is the primary growth, however small. Testicular involvement has been excluded with certainty in this case, as it has in but a few others, notably Cases V and VI in the series abstracted from the literature.

What then concerning histogenesis? Certainly those cases in which there is an associated teratoma present less difficulty. No such feature was present in this case. The theory of origin from the urogenital anlage is attractive, especially in view of the origin of this growth in the retroperitoneal tissue immediately adjacent to the kidneys, though sufficient proof of this concept is lacking.

Summary

Review of the literature has disclosed 131 cases of chorionepithelioma in the male, more than 90 per cent of which arose primarily in the testicle. In some the origin is doubtful, but at least seven recorded cases seem to be definitely of extragenital origin, and to these is added an eighth case, herewith described. This was a tumor of chorionepitheliomatous structure arising in the retroperitoneal tissue of a man forty years of age. Of the numerous theories of histogenesis, that assigning the origin to the urogenital anlage appears to be the most satisfactory explanation in this case.
Bibliography

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