



GESTATIONAL TROPHOBLASTIC NEOPLASMS: A Century of Progress

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Although still encountered today, the diagnosis of gestational trophoblastic neoplasm does not portend the same grave prognosis as it did 60 years ago. When in 1955 Hunter and Dockerty published their case series, 10 of 13 patients succumbed to the disease, including:

A 23-year-old gravid II, para II came to the clinic in September, 1949, with known pulmonary metastasis. The patient had born 2 children; the second, a normal full-term infant, had been born in January, 1949. One month later, sudden profuse vaginal hemorrhage occurred. Daily bleeding had persisted in spite of dilatation and curettage done in March and again in July, 1949. No identifiable tissue was obtained on either occasion. On August 20, 1949, results of a Friedman test were positive. On September 15, 1949, hysterectomy was done. Pathology diagnosis was choriocarcinoma....

Hemoptysis was noted after operation and roentgenograms of the thorax revealed multiple pulmonary metastatic lesions. On examination at the clinic, a semisolid bluish mass was noted at the introitus; this undoubtedly represented a vaginal metastatic tumor...palliative roentgen therapy to the thorax and pelvis was begun...stopped after several days because of profuse vaginal bleed-

ing. The patient was allowed to go home to be with her family; death occurred in November, 1949.¹

The above case vignette is classic for its day. Choriocarcinoma struck the young, often following a normal pregnancy, with almost always fatal outcomes within a few months of diagnosis. Today, it is relatively rare that a patient in the developed world dies from this process, a triumph of modern oncologic gynecologic care. And yet, its history does not represent the typical inevitable march of progress. Gynecologists first had to identify the disease process itself; collaborate through the construction of tumor registries; construct feasible treatment plans, initially surgical only and later chemotherapy; and ultimately standardize terms and staging procedures.

LABELING OF THE DISEASE

Trophoblastic tumors were described by the ancient writers. Aetius of Amida, a 6th-century physician at Justinian's court, is given credit for coining the term "hydatid." One of the earliest illustrations of the disease can be found in the textbook *La pratique des accouchemens soutenue d'un grand nombre d'observations* by Paul Portal in 1685 (Figure 1).² In the intervening years, numerous case reports of possible molar pregnancies were published, with various theories as to their origin.

The modern history of choriocarcinoma begins in 1889. Previously, early pathologists believed these to be unusual examples of primary carcinoma of the uterus. However, Max Sanger, a prominent German ObGyn, thought otherwise. In his publica-

FOCUSPOINT

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tion, Sanger provided a brief account of 2 cases of miscarriage and correlated the clinical findings of postabortal hemorrhage, cough, and dyspnea with the gross pathology finding on autopsy of a spongy uterine tumor, which appeared like a “sarcoma telangiectoides” and microscopic findings of multinucleated, nonepithelial cells.³ Therefore, “deciduoma malignum” was not an ordinary sarcoma of the uterus but rather a growth originating from the decidua.

Sanger’s theory that the tumor was a sarcoma was based on its origin at the placental site. He considered the decidual cells to be the essential malignant cells, while the presence of the chorionic cells was thought to be adventitious. For the next 5 years, Sanger’s theory held sway. However, in 1894, Sigmund Gottschalk dissented and emphasized that the disease was primarily of fetal origin, being a sarcoma of the chorion.

Gottschalk’s insistence on the dominant participation of chorionic elements set the stage for the development of Felix Marchand’s theory, first published in 1895. Reporting on 2 case studies, as well as a literature review of 26 additional cases, Marchand

demonstrated that these tumors were invariably the sequel to normal pregnancy, abortion, hydatidiform mole, or ectopic pregnancy; and he concluded that the tumors were epithelial in nature, tracing their histogenesis to the chorionic villi and thereby coining the term chorionepithelioma.⁴ But it is one thing to understand the origin of disease and quite another to treat it.

For the next 60 years, physicians continued to struggle with its management. Kelly’s classic textbook, published in 1908, identifies “Chorio-epithelioma or deciduoma malignum, [as] a new growth developing after a normal pregnancy, an abortion, or the expulsion of a hydatidiform mole.”⁵ But there was no discussion as to management; other than hysterectomy, there was none.

By the time Munro Kerr’s *Combined Textbook of Obstetrics & Gynecology* (1946) (Figure 2) came out with its fourth edition, management had evolved slightly. “The presence of metastatic deposits in the lungs or elsewhere renders the prognosis very grave. Nevertheless, if the pelvic disease can be removed this should be done, even under discouraging conditions, for it occasionally happens that the secondary deposits disappear after the removal of the parent growth...In inoperable cases X-rays and radium may be employed.”⁶ But as the prior vignette relates, radiotherapy was typically not successful. Cases of spontaneous regression were reported, but the mortality rate remained above 90% for those with metastatic disease. What was needed was a greater understanding of the disease process, which could only occur with a pooling of resources.

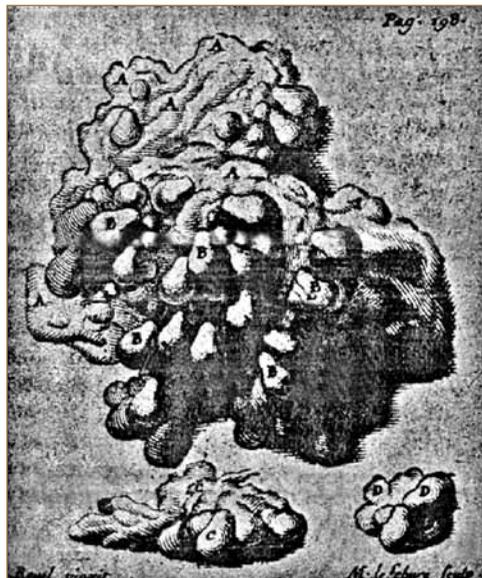


FIGURE 1. Molar pregnancy. Reprinted from Longo LD. Classic pages in obstetrics and gynecology. Some observations on non-malignant conditions of the cervix. Vithal Nagesh Shirodkar. *Journal of Obstetrics and Gynaecology of India*, vol. 3, pp. 287-289, 1953. *Am J Obstet Gynecol.* 1979;133(1):81-82, with permission of Elsevier.

TUMOR REGISTRY

In September 1946, the American Association of Obstetricians, Gynecologists and Abdominal Surgeons created the Albert F. Mathieu Chorionepithelioma Registry. Mathieu, a former vice president of the earlier ACOG, was also an associate professor at the University of Oregon Medical School. Following his death in 1939, his friend and colleague Albert Holman proposed a memorial registry dedicated to Mathieu’s primary passion. A committee was named, with Emil Novak as chairman. Novak stressed that the primary purpose of the

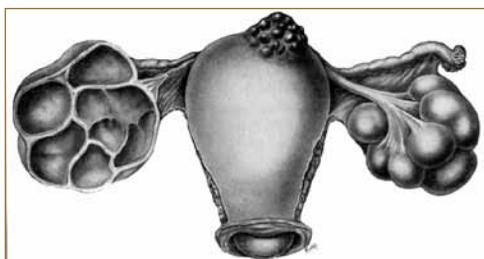


FIGURE 2. Chorionepithelioma. Reprinted from Munro Kerr JM. *Combined Textbook of Obstetrics and Gynecology*. Edinburgh: E&S Livingston Ltd; 1946:987.

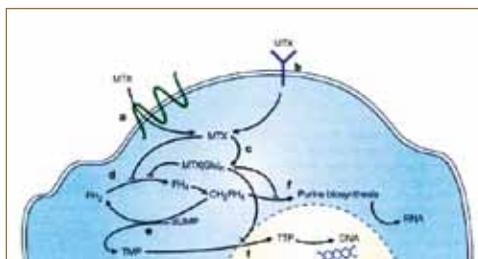


FIGURE 3. Methotrexate. Reprinted from Chabner BA, Roberts TG. Timeline: Chemotherapy and the war on cancer. *Nat Rev Cancer*. 2005;5(1):65-72, with permission of Elsevier.

registry was not to provide a rapid diagnostic service. Instead, through the accumulation and authentication of submitted materials, a better understanding of the clinical and pathologic characteristics of chorionepithelioma and hydatidiform mole would be achieved.

When a specimen was received, Novak would read the slides and make a preliminary diagnosis. He would then send the slides to committee members in turn, asking each to make a diagnosis and return the slides to him. The committee would resolve differences and come to a final diagnosis. A follow-up on all living patients was made every year.

By 1949, the registry had received a total of 85 cases, of which 21 were authentic chorionepitheliomas.⁷ The value of a central registry lay in the standardization of diagnostic criteria, ultimately allowing clinicians to identify prognostic criteria and possibly a cure. Nonetheless, while clinicians were becoming better at predicting who might develop chorionepithelioma, the mortality rate remained high.

CHEMOTHERAPY

Paul Ehrlich coined the term “chemotherapy” and applied it to his treatment of syphilis. Others adopted the term and expanded the concept to include medical therapies for cancer. But it wasn’t until the advent of molecular medicine during the latter half of the 20th century, when the biological mechanisms of transformation and tumor progression were understood, that the treatment of cancer evolved from primarily a surgical specialty into a multidisciplinary approach and chemotherapy truly came into its own. The history of choriocarcinoma

is intricately entwined with the evolution of chemotherapy.

Following World War II and the success of the new antimicrobial agents in the treatment of lethal infectious diseases, hopes were raised that cancer could be as easily addressed. Funds were released to researchers interested in investigating the cytotoxic effects various agents had on tumor suppression. The discovery of amethopterin was an early success story. In the late 1920s, folic acid and its role in metabolism were discovered by Lucy Wills, a medical missionary working in India. Wills showed that a yeast extract could correct the macrocytic anemia in her patients.⁸

Subsequent studies revealed the structure of folic acid and ultimately led to the research and biosynthesis of antagonists; the most notable were aminopterin and amethopterin, later known as methotrexate (Figure 3). By utilizing the principle of a biologic antagonist working at a specific point within a cell cycle, Sydney Farber provided the medication to patients suffering from acute lymphoblastic leukemia with favorable, though limited, results. Methotrexate, thereby, demonstrated that antifolates could suppress proliferation of malignant cells.

Others, including Min C. Li, studied the effect of these antifolates on other cancers. In a fortuitous observation, Li noticed that while treating a metastatic melanoma patient with methotrexate, her elevated urinary beta hCG levels fell dramatically. Concurrently, Roy Hertz (Figure 4) published his account of the stimulation of growth of the chick oviduct with estrogen, an effect which could be inhibited by the antifolate aminopterin.⁹



FIGURE 4. Roy Hertz, MD (1909-2002). Reprinted from Yarris JP, Hunter AJ. Roy Hertz, M.D. (1909-2002): the cure of choriocarcinoma and its impact on the development of chemotherapy for cancer. *Gynecol Oncol.* 2003;89(2):193-198, with permission of Elsevier.

In 1955, Hertz invited Li to join him at the National Institutes of Health (NIH). "Since choriocarcinoma is of fetal origin, I thought that there might be a chance that methotrexate could cause regression of a fetal tumor such as metastatic choriocarcinoma."¹⁰ Within 2 months, Li and Hertz had the opportunity to test their theory concerning the efficacy of methotrexate, when the wife of a naval officer presented to the NIH with metastatic pulmonary disease. She was given an initial dose of 10 mg IV. "To everyone's surprise, the patient survived the ensuing 20 hours."⁹

Subsequent doses followed, and 4 months later the patient was normal, without evidence of disease. This was the first solid tumor in humans to be cured by drug therapy. Chemotherapy had arrived. By 1961, Hertz was able to publish the results of 63 patients and "establish the substantial therapeutic value of intensive chemotherapy in women with metastatic tumors of trophoblastic origin."¹¹ Moreover, his studies also established standard doses and identified common drug side effects and toxicities. By 1962, the cure rate of the previously fatal choriocarcinoma had significantly improved to about 80%.

CYTOGENETICS AND PATHOGENESIS

While therapy for choriocarcinoma was being devised by Hertz and Li, others attempted to understand the pathogenesis of the disease. At mid-century, many believed that retention of a blighted ovum with cessation of the villous stromal circulation and continued secretory activity of the trophoblast resulted in hydropic degeneration of the villous stroma and sub-

sequent trophoblastic proliferation. However, interesting reports based upon the new discipline of cytogenetics were appearing.

As early as 1962, Atkin and Klinger reported a case of a hydatidiform mole associated with a triploid chromosomal complement (3A/XXX).¹² Subsequent studies by Makino, Carr, Baggish, and their colleagues established the presence of a sex chromatin in nearly all hydatidiform mole cases.¹³⁻¹⁵ And by 1980, based upon the works of Vassilakos, Szulman, and Kajii, a complete understanding of pathogenesis was made.¹⁶⁻¹⁸

Hydatidiform moles may be classified into 2 entities with distinct pathologic and genetic features. The complete mole shows cystic swelling and gross trophoblastic proliferation in the absence of any evidence of fetal development. By chromosomal analysis, these have been shown to be diploid, almost always XX and androgenic in origin. By contrast, the partial mole shows focal trophoblastic hyperplasia and is associated with the presence of a fetus at some stage; these moles have been shown to be triploid. Choriocarcinoma, like true malignant tumors, exhibits aneuploidy.

CONCLUSION

By 1989, or 100 years after Sanger's original publication, gynecologists had expanded their knowledge of choriocarcinoma beyond the primitive "to cut is to cure" mantra. Tumor registries permitted the establishment of diagnostic criteria and, indirectly, prognostic tools. Government funding, in the form of NIH grants, unleashed a flurry of research targeting cancer and, in particular, the development of treatments. International bodies, such as the World Health Organization and the International Federation of Gynecology and Obstetrics, similarly contributed by demanding standardized terminology and staging systems, thereby permitting a rational approach to treatment.

Today, gestational trophoblastic neoplasm is recognized as one of the most curable diseases. But more importantly, its cure represents the collaborative efforts

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from multiple disciplines, focused upon the betterment of women's health care.

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