103. A Further Cytogenetic Study of Hydatidiform Mole, with Reference to its Androgenetic Origin

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Based on gross morphology, histopathology, and karyotype, Vassilakos, Riotton and Kajii (1977) divided specimens with swellings of the chorionic wall into two entities of different origin; partial and complete moles. Karyologically the majority of cases in the former category was characterized by heteroploid constitution involving triploidy and trisomies, whereas the latter was exclusively provided with a normal female karyotype, 46,XX. These two entities were morphologically distinct from each other. Complete moles with villi consisting of pronounced hyperplastic and anaplastic trophoblasts have no fetus, cord, or amniotic membrane, while partial moles do not show marked trophoblastic hyperplasia or anaplasia. Such chorionic lesions have been a subject of special attention primarily on account of possible malignant transformation into choriocarcinoma.

Current cytogenetic investigations have presented interesting evidence showing that complete moles are androgenetic in origin (Kajii and Ohama 1977; Wake et al. 1978; Jacobs et al. 1978). The chromosome findings were compatible with views of either fertilization by a diploid sperm resulted from nondivision at the second meiotic division, or fertilization by a haploid sperm followed by duplication of its chromosomes. This sequence leads to the preponderance of 46,XX karyotype in moles, since YY specimens are nonviable and lost during early stages of the cleavage. However, it cannot be excluded that other mechanisms would be possibly contribute to the formation of complete moles. In this context, some familial analyses of polymorphic variants have been undertaken by us in newly obtained six cases of molar conceptuses, findings of which are dealt with in this article.

Materials and methods. Molar tissues were removed from 13 patients by means of dilatation and curettage of the uterine cavity. These specimens were determined as complete moles on the basis of criteria approved by the Chorionic Tumor Committee of the Japan Society of Obstetrics and Gynecology (1978). They were cultured in Eagle’s minimal essential medium supplemented with 20% fetal calf serum in an atmosphere of 5% CO₂ in air. Peripheral blood samples
from parents were cultured in a conventional manner. Air-dried slides from these cultures were stained with quinacrine mustard, and examined by means of fluorescence microscopy.

Results. Cultures from six mole specimens yielded metaphase cells available for analyses of chromosome polymorphisms. The cases under study were exclusively characterized by a normal female karyotype (46,XX) and their parents were also chromosomally normal. In one case the quality of the preparation was not suitable for analyses of polymorphic chromosome variants, except for the confirmation that the karyotype of this case was 46,XX.* We had other 6 cases which failed to grow.

Six pairs of marker chromosomes (nos. 3, 13–15, 21–22) were scored for Q-band polymorphisms in cells from both moles and their parents. The Q-banded chromosomal features in cells from 6 moles were outstanding in having uniform homozygosity in members of each pair. In contrast, the parental karyotypes had at least 1 of 6 pairs which was heterozygous in Q-banding. Comparison of polymorphic markers between cells from molar conceptuses and their parents, except case 2, provided the results that neither of the maternal homologues was transmitted to moles in 10 identified pairs of chromosomes, and both members of 8 homologues identified in moles were traceable only to one of the corresponding paternal homologous chromosomes (Fig. 1). These findings are highly suggestive of that these moles have received a paternal haploid set in duplicate, but none from the mother. In the exceptional case 2, any polymorphic feature was absent between the mole and its parents to determine the parental origin of the 6 pairs in the former. However, homomorphism shown by this mole leads to the suggestion that it is also of androgenetic origin. Thus, the present study resulted in the confirmation of the previous data provided by Kajii and Ohama (1977), Wake et al. (1978) and Jacobs et al. (1978), in favor of the view that androgenesis is a cause of complete moles.

Remarks. The literature refers to three cytogenetic papers regarding complete moles in which the presence in duplicate of a paternally derived haploid set was verified by the use of chromosome polymorphisms (Kajii and Ohama 1977; Wake et al. 1978; Jacobs et al. 1978). It has been demonstrated in these studies that a total of 20 cases of complete moles including present ones is androgenetic in origin. Recently we undertook a study with HLA absorption in molar tissues, and resulted in that 13 molar tissues expressed homozygous HLA-A and -B specificities which were inherited only from the father.

* Recent studies by Ichinoe resulted in that 57 cases of hydatidiform moles under study had a 46,XX chromosome constitution without exception.
but none from the mother (Yamashita et al., unpublished). The evidence here presented suggests that androgenesis is responsible for the pathogenesis of most, if not all, cases of complete moles. However, we are aware of three cases with an XY complex reported so

![Fig. 1. Chromosome polymorphisms indicating differences between moles and their parents. A paternal chromosome was transmitted in duplicate to the mole in no. 22 of case 1; nos. 13, 14, 21 of case 3; nos. 13, 14 of case 4; nos. 15, 21 of case 5 and nos. 15, 21 of case 6. None of the maternal homologues was transmitted to the mole in no. 21 of case 3 and no. 21 of case 4.](image)
far in the literature (Sasaki et al. 1962; Bourgoin et al. 1965; Shinohara et al. 1971). Kajii and Ohama (1977) also observed three X chromatin-negative moles; two were Y chromatin-negative, and one was Y chromatin-positive in 54% of its stromal cells. Kajii and Ohama (1977) proposed the view that the abnormal first meiotic division in the male would result in XY diploid sperm, which in turn could produce XY moles. Familial analysis with polymorphic chromosome variants will be essential in such cases, and another mechanism might be expected by those investigations for the genesis of complete moles in future.

The presence of paternally derived marker chromosomes in duplicate suggests that the doubling of a paternal haploid set had occurred either after fertilization, or otherwise at the second meiotic division. Homozygous expression of HLA-A and -B specificities as revealed in the molar tissues (Yamashita et al. unpublished) favors the view that most of complete moles may arise from the former mechanism. In such a case, the duplication of a paternal haploid set might have occurred either at or after the first cleavage division. The mosaic consisting of haploid and diploid cells may be expected in the latter case, though the haploid cells may be eliminated during the course of growth. Details will be reported in near future.

Androgenetic ova have occasionally been reported in rats and mice at the pronuclear stage (Austin and Braden 1954; Takagi unpublished). Various experiments with mice have been attempted to develop the fertilized egg, in which uniparental (maternal or paternal) genome is retained. Recent investigations applying microsurgical techniques are of special interest in this connection; the experiments through the removal of one pronucleus shortly after fertilization (Markert and Petters 1977), or the bisection of the fertilized egg at the pronuclear stage (Tarkowski 1977), rarely resulted in the production of blastocysts. Further, the recent experiment of Hoppe and Illmensee (1977) has indicated that viable homozygous-uniparental diploid mice can be generated by microsurgically removing one pronucleus from the fertilized egg and diploidizing the residual one in the presence of cytochalasin B. These mice were reported to be fertile. Further studies are needed on the nature and behavior of androgenetic ova which are different between men and mice.

Kajii and Ohama (1977) postulated a recessive mutation of a gene (or genes) controlling cell growth for the frequent neoplastic transformation of moles into choriocarcinoma. Exclusive transmission of paternal genome in choriocarcinoma cells present before us a serious question why such an allogeneic tumor grows progressively in the maternal body. One of the reasons for this may be possible that
major histocompatibility antigens are not expressed on the trophoblasts, though Tsuji et al. (in press) recognized that the expression of HLA in the trophoblasts is as much the same as in other cellular components of the mole. Recently we investigated the chromosomes of 4 cases of primary and metastatic chorionic tumors, and found that they were characterized by a high incidence of cells in the tetraploid range, and that homologous chromosomes of certain pairs with polymorphic chromosome variants were not morphologically identical (Wake unpublished). Thus, the above data seem to be unfavorable for the view of cellular continuity between moles and choriocarcinoma, though tumors have been clinically assumed to be preceded by molar conception.

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References