The diagnosis of trophoblastic tumours from uterine curettings¹

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SYNOPSIS The reliability of the diagnosis of choriocarcinoma from uterine curettings is still a matter for debate, and few pathologists see enough material for an objective clinico-pathological study. In the present survey curettings from 54 patients were examined, 38 during follow up of a hydatidiform mole, 12 following a normal pregnancy and four after a spontaneous abortion. Four histological categories were identified: villous, simple trophoblast, trophoblast with appearances suspicious of choriocarcinoma, and trophoblast diagnostic of choriocarcinoma. The presence of hydropic villi is evidence that malignant change has not developed at that time and only two of the 20 patients in this group subsequently developed choriocarcinoma. The interpretation of simple or suspicious trophoblast depends on the antecedent gestation: if it were molar, malignant change is relatively infrequent (choriocarcinoma subsequently developed in four out of 15 patients); if it were non-molar then malignancy is a strong possibility (choriocarcinoma developed in nine and metastatic trophoblastic disease in four of the 13 patients). The correct management of the individual patient can only be achieved by a full consideration of the histological features together with the clinical history and findings.

Uterine curettings containing chorionic villi or fragments of trophoblast are commonly encountered in routine histopathological practice. Most are simple retained products of conception, but in some the trophoblast appears abnormal and the possibility of choriocarcinoma must be considered. The accuracy of the diagnosis of choriocarcinoma from curettings is still debated, partly due to cases in which curettage fails to produce trophoblastic tissue, but also because of difficulties in the interpretation of curettings in which trophoblast is present (Novak, 1922; Mathieu, 1939; Hammond, Hertz, Ross, Lipsett, and Odell, 1967). However, several authors (Teacher, 1935; Park and Lees, 1950; Sta. Cruz, 1959) have found curettage to be useful in some cases, while Novak and Seah (1954) showed that in 13 of 74 cases of choriocarcinoma the diagnosis was strongly indicated by examination of uterine curettings. Because of the rarity of choriocarcinoma in the United Kingdom the experience of most pathologists is limited and there is a tendency towards overdiagnosis of malignancy. The purpose

of this paper is to present the results of a clinico-pathological study of curettings from a large number of patients with trophoblastic disease, to define the histological diagnostic criteria, and to suggest general principles for the reporting of such specimens.

Materials and Methods

Uterine curettings from 54 patients treated at Fulham Hospital between 1958 and 1969 were examined. In 38 patients the curettings were obtained during follow up of a hydatidiform mole, in 12 following a normal pregnancy, and in four after a spontaneous abortion. Two separate curettages were performed in 11 patients following a hydatidiform mole, two following a normal pregnancy, and two after an abortion, with three separate curettings in one patient after a normal pregnancy, giving a total of 71 specimens. The patients were aged between 17 and 33 years. Forty-four were alive at the time of the study, survival times ranging from three to seven years. The methods of treatment included surgical excision of tumours, chemotherapy, and ionizing radiation (Bagshawe, 1963, 1967a, 1967b, 1969; Bagshawe and Wilde, 1964). Paraffin sections of the

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curettings were cut at 5 μ m and stained with Cole's haematoxylin and 1% aqueous eosin Y. Multiple levels from each block were examined where necessary. All material was examined without knowledge of clinical details.

Results

Initially sections were examined and classified purely on histological criteria. Subsequently a clinico-pathological correlation was made.

MAIN HISTOLOGICAL FINDINGS

Choriocarcinoma is typically composed of large sheets of invasive trophoblast which tend to be organized into central cores of cytotrophoblast surrounded by peripheral rims of syncytiotrophoblast outlining pseudo-intervillous spaces (Fig. 1). Chorionic villi are not present. These appearances were used as a basic guide in the study, and from a preliminary examination of the sections four histological categories were established.

Fig. 1 Trophoblast with appearances diagnostic of choriocarcinoma. The typical organized pattern is seen with syncytiotrophoblast lining pseudo-intervillous spaces containing red cells. Haematoxylin and eosin $\times 300$.

Villous

Hydropic chorionic villi (Fig. 2) were found in sections from 25 curettings. In some cases most of the tissue was villous, whilst in others only occasional small villi were found after searching several sections. The degree of trophoblastic hyperplasia was also variable and in some cases the villi were overshadowed by large sheets of trophoblast (Figs. 3 and 4).

Simple trophoblast

The trophoblastic tissue in 13 specimens was in this category. There were two main features, the fragments of trophoblast being small and scanty and differentiation into cytotrophoblast and syncytiotrophoblast poor (Fig. 5). Small fragments of syncytiotrophoblast alone were commonly found, while in some specimens a 'tissue-culture-like' growth around and within blood clot was observed. Nucleoli were not prominent, but nuclei were often hyperchromatic and irregular in size and shape, appearances which could lead the unwary into a mis-

Fig. 2 Villous trophoblast. There is hydropic degeneration of the stroma of chorionic villi, with slight trophoblastic hyperplasia. H & E $\times 75$

Fig. 3 Part of a postmolar curetting in which the hyperplastic trophoblast resembles choriocarcinoma in structure. *H & E* $\times 120$

Fig. 4 A different area of the curetting shown in Figure 3. There are small hydropic chorionic villi, making a diagnosis of choriocarcinoma untenable. *H & E* $\times 80$

Fig. 5 Simple trophoblast. Small fragments of blood clot and trophoblast with hyperchromatic irregular nuclei. However, there is no clear differentiation into cytotrophoblast and syncytiotrophoblast. *H & E* $\times 80$.

Fig. 6 *Suspicious trophoblast. Although cytotrophoblast and syncytiotrophoblast can be identified separately, the overall pattern is disorganized. H & E $\times$ 75.*

Fig. 7 *Placental site reaction showing 'wandering giant cells' in the myometrium deep to the implantation site. H & E $\times$ 120*

Fig. 8 *Exaggerated placental site reaction in myometrium showing mononuclear and multinucleated trophoblastic cells infiltrating between muscle bundles. Curetting following a spontaneous abortion. H & E $\times$ 160*

diagnosis of malignancy. There was no evidence of invasion and chorionic villi were not present.

Trophoblast with appearances suspicious of choriocarcinoma

In 20 curettings the appearances of the trophoblast were intermediate between those of simple trophoblast and trophoblast diagnostic of choriocarcinoma. In all the specimens there were moderate to large sheets of trophoblast; differentiation into cytotrophoblast and syncytiotrophoblast was always seen, but varied between cases in which the overall pattern was disorganized (Fig. 6) and those in which it more closely resembled the orderly structure of choriocarcinoma. In none of the curettings was there evidence of trophoblastic invasion. Chorionic villi were not present.

Trophoblast with appearances diagnostic of choriocarcinoma

In 13 specimens the appearances were diagnostic of choriocarcinoma. There was invasion of endometrium and myometrium by large sheets of cytotrophoblast and syncytiotrophoblast with the typical well organized pattern of choriocarcinoma (Fig. 1). Nuclei were vesicular, with prominent and often multiple nucleoli. Chorionic villi were not present.

OTHER HISTOLOGICAL APPEARANCES

Apart from the groups described above, another histological category, placental site reaction, was seen with sufficient frequency to warrant inclusion as a source of diagnostic difficulty. A moderate number of so-called 'wandering trophoblast cells' at the site of placental implantation, as in Fig. 7, is a normal physiological finding, but the appearances shown in Fig. 8 are an exaggeration of the normal. Because of the myometrial infiltration by trophoblastic cells both pictures, and especially the exaggerated reaction, may be confused with choriocarcinoma.

CLINICO-PATHOLOGICAL CORRELATION

Table I shows the distribution of the histological categories in groups according to the antecedent gestation.

In this part of the study histological findings were related to subsequent trophoblastic disease in two groups of patients, those whose curettings were obtained after a hydatidiform mole (molar group) and those in whom curettage was performed after a normal pregnancy or abortion (non-molar group).

The number of patients in each category of subsequent trophoblastic disease is shown in Table II. The choriocarcinomas and invasive moles were all

Histological Group	Hydatidiform Mole	Normal Pregnancy	Abortion	Total
Villous	25	0	0	25
Simple trophoblast	11	0	2	13
Suspicious trophoblast	7	11	2	20
Diagnostic of choriocarcinoma	6	5	2	13
Total	49	16	6	71

Table 1. Number of biopsies in each histological category related to antecedent gestation

Subsequent Trophoblastic Disease	No. of Patients
Choriocarcinoma	21
Invasive mole	3
Persistent trophoblastic proliferation	
Metastatic	10
Non-metastatic	18
Nil	2
Total	54

Table II. Subsequent trophoblastic disease in 54 patients studied

diagnosed on clinical, hormonal, and radiological criteria, and confirmed histologically. In the category 'persistent trophoblastic proliferation' there was clinical and hormonal evidence of continued trophoblastic growth but no firm histological diagnosis was made. The presence of metastases was assessed radiologically. Both cases in the 'nil' group followed hydatidiform moles and neither had evidence of continued trophoblastic proliferation after curettage.

The relationships between histological group and subsequent trophoblastic disease were as follows:

Villous

Twenty-five curettings from 20 patients contained molar villi. In all patients the antecedent gestation was a hydatidiform mole. In one of these patients (case 94) a previous curetting had contained only simple trophoblast and this case is considered in the next section. The subsequent trophoblastic disease in the remaining 19 patients is shown in Table III. Only two patients were later shown to have developed

Choriocarcinoma	Invasive Mole	Persistent Trophoblastic Proliferation			Total
		Metastatic	Non-metastatic	Nil	
2	2	3	11	1	19

Table III. Subsequent trophoblastic disease in 19 patients whose curettings contained villous trophoblast

choriocarcinoma. Of the remaining 17, four needed no further treatment and 13 were given short courses of chemotherapeutic agents (methotrexate and 6-mercaptopurine for less than four months). There was one death, in a patient with choriocarcinoma, and the other 18 are alive and well.

Simple and suspicious trophoblast

Since the distribution of subsequent trophoblastic disease was the same in both categories they were combined into a single group. There were 33 curettings from 29 patients. In one patient a repeat curetting revealed villous trophoblast (case 94—case history given below), and there were therefore 28 cases suitable for analysis. The influence of the antecedent gestation on the subsequent trophoblastic disease in these patients is shown in Table IV. There is a clear difference between the two groups in the number of patients who were later found to have choriocarcinoma, four out of 15 (26%) in the molar group and nine out of 13 (69%) in the non-molar group. Further, all the non-molar patients developed malignant or metastatic trophoblastic disease necessitating treatment with chemotherapeutic agents, and despite this four patients died. Conversely, only eight (52%) of the molar patients were in the malignant or metastatic category with one death, while of the remaining seven patients three required no chemotherapy at all.

The relationship between antecedent gestation and subsequent trophoblastic disease is further illustrated by the following case histories:

Case 245, Mrs D.G., 24 years

Six weeks after a normal pregnancy this patient started to lose fresh blood per vagina. Because the blood loss persisted a curettage was performed two weeks later. The histological appearances were thought to be suggestive of choriocarcinoma and the section was referred to us for opinion. Although suspicious, the trophoblast was not diagnostic of choriocarcinoma (Fig. 6). But, since the antecedent gestation was a normal delivery, there was a strong possibility that malignant change had occurred and

the patient was referred for clinical assessment. Her gonadotrophin excretion was 250,000 IU HCG/24 hr (normal < 100 IU HCG/24 hr) and radiographs of the chest showed multiple metastases. From the above evidence a clinical diagnosis of choriocarcinoma was made, and the patient was treated with chemotherapeutic agents. She remains well two years later.

Case 171, Mrs B.E., 18 years

Following the abortion of a hydatidiform mole at 17 weeks' gestation this patient remained well and symptomless for two months. She then noticed a bloodstained vaginal discharge, but thought that this was a normal menstruation. The haemorrhage continued and curettage was performed a month later. This revealed simple trophoblast. The patient was managed conservatively and over the next two months her previously raised urinary gonadotrophin levels (3,217 IU HCG/24 hr) fell to normal. No treatment was required.

Case 94

The case history of the separate patient in this group, Mrs. E. McC. (case 94) is as follows: At 13 weeks' gestation this primigravida, aged 17 yr, aborted a hydatidiform mole. Because of persistent vaginal bleeding a curettage was performed 10 days later. Sections showed simple trophoblast with no evidence of chorionic villi. Fortunately hysterectomy was not performed, for three weeks later, following a further haemorrhage, curettage revealed villous trophoblast. Later, because her gonadotrophin excretion remained abnormal six courses of methotrexate and 6-mercaptopurine were given over a 10-week period, and the patient is alive and well five years later.

Trophoblast diagnostic of choriocarcinoma

Thirteen curettings containing trophoblast diagnostic of choriocarcinoma were obtained from 11 patients. This includes five patients in whom previous curettings had contained simple or suspicious trophoblast. In five patients the antecedent gestation was a

Patients		Subsequent Trophoblastic Disease				
		Choriocarcinoma	Invasive Mole	Persistent Trophoblastic Proliferation		
				Metastatic	Non-metastatic	Nil
Molar	15	4	1	3	6	1
Non-molar	13	9	0	4	0	0
Total	28	13	1	7	6	1

Table IV Subsequent trophoblastic disease in 28 patients with simple or suspicious trophoblast in curettings related to antecedent gestation

hydatidiform mole, in four a normal pregnancy, and in two an abortion. There were two deaths, and the other nine patients are alive and well.

In the whole series it was possible to make a positive histological diagnosis in only 20% of the cases (11 out of 54). Ten further patients were subsequently shown to have choriocarcinoma, five at hysterectomy and five at necropsy, an overall figure of 38%.

Time interval between antecedent gestation and curettage

The time intervals between antecedent gestation and curettage are shown in Table V. The cases were divided for this purpose into two groups, those with villous and those with non-villous curettings (simple, suspicious, and diagnostic trophoblast). More than 50% of all curettings were obtained within three months of the gestation but in nearly 15% the time interval was longer than seven months, the longest being 14 months.

Time Interval in Months	Number of Biopsies		
	Villous	Non-villous	Total
<1	10	7	17
1-3	8	12	20
3-5	4	10	14
5-7	1	9	10
>7	2	8	10
Total	25	46	71

Table V Distribution of villous and non-villous curettings according to time interval between antecedent gestation and curettage

Discussion

This study shows that there are two main principles which must be followed in the assessment of curettings containing trophoblast. A precise obstetric history must be obtained and a thorough examination made of the histological material. The appearances of the latter can be divided into three main groups: villous, simple or suspicious trophoblast, and trophoblast diagnostic of choriocarcinoma.

In this series all the curettings containing chorionic villi were obtained after abortion of a hydatidiform mole. It is not unusual to find villous trophoblast in curettings taken after a normal pregnancy or an abortion, but the question of abnormal trophoblastic proliferation seldom arises, as any trophoblast which persists is usually in the form of degenerate chorionic villi, the so-called retained products of conception. After a hydatidiform mole the problem is more difficult because of the increased malignant potential, estimated at between two and

four thousand times that of a normal pregnancy or simple abortion (Park, 1959). Nevertheless, the present results show that the finding of villi in a postmolar curetting was an indication that choriocarcinoma had not developed at that time, and in only two of the 19 patients was a positive diagnosis of choriocarcinoma ever established. The presence of an invasive mole cannot be excluded when villous curettings are found, and two patients later underwent hysterectomy at which an invasive mole was found. However, these two patients and the remaining 15 patients in the group pursued a relatively benign course, four needing no further treatment and 13 requiring only short courses of chemotherapeutic agents. It is therefore unjustified to make a positive diagnosis of choriocarcinoma from curettings containing villous trophoblast. The histological report should be descriptive, recording the presence of villi, with a conclusion of persistent hydatidiform mole. This does not mean that the presence of villi has no significance. A meticulous follow up must be undertaken, with regular urinary gonadotrophin assay and clinical assessment, as a proportion of the patients will need chemotherapy either because of continuing symptoms, metastases, a rising gonadotrophin excretion, or persistence of trophoblast for more than six months after evacuation (Bagshawe, Golding, and Orr, 1969).

It follows that in the examination of uterine curettings containing trophoblast a thorough search for chorionic villi is essential. All available material should be embedded and multiple sections examined if necessary. Villi may be very small and easily missed, or the trophoblastic hyperplasia so resemble choriocarcinoma that the villi are overlooked or assumed to be of no significance (Figs. 4 and 5).

Although most of the curettings containing villi were obtained within three months of abortion of the hydatidiform mole, in some, longer periods had elapsed, the longest being nine months. Molar tissue can therefore persist in the uterus for a long time, indicating that even if villi are not found in a curetting, persistent hydatidiform mole cannot entirely be excluded (see case 94 in which villous trophoblast was found after a previous curetting had shown simple trophoblast).

When the subsequent trophoblastic disease is considered in those patients whose curettings contained simple or suspicious trophoblast the type of antecedent gestation is seen to be of great importance (Table IV). The percentage of patients in the non-molar group who developed choriocarcinoma was nearly three times that in the molar group. Furthermore, all the patients in the non-molar group had malignant or potentially malignant disease necessitating chemotherapy, while nearly

half of the molar patients pursued a relatively benign course and three required no chemotherapy. Thus the finding of simple or suspicious trophoblast in a curetting following a normal pregnancy or abortion is a strong indication that malignant trophoblastic disease has developed, whilst the same histological appearances after a hydatidiform mole should be regarded with caution. Careful follow up is essential but a definite histological diagnosis cannot be made. Although a proportion of the patients will need prophylactic chemotherapy, the overall aim should be conservative treatment where possible. Over-diagnosis of malignancy by the pathologist may lead to unnecessary hysterectomy.

These points are well illustrated by the case histories quoted previously. In the first case (case 245), using the premise that all non-villous trophoblast found after a normal pregnancy or abortion is potentially malignant, it was possible to institute urgent clinical assessment and thus initiate early treatment. In the second case (case 171) because the previous gestation was a hydatidiform mole caution prevailed and treatment was withheld. If other factors such as urinary gonadotrophin excretion had later indicated continued proliferation of trophoblast, then treatment with chemotherapeutic agents could have been given.

It must be reiterated that before a curetting is accepted as diagnostic of choriocarcinoma all the histological criteria, particularly invasion by trophoblast and absence of chorionic villi, must be fulfilled. Even if the appearances are thought to be diagnostic extra care should be taken if the previous gestation was a hydatidiform mole. Placental site reaction is the commonest source of diagnostic difficulty, and the appearances are often confused with those of choriocarcinoma. However, in placental site reaction the organization of both trophoblastic elements seen in choriocarcinoma is lacking and mononuclear or multinucleated trophoblastic cells infiltrate singly or in cords between muscle bundles. The exaggerated reaction, often referred to as 'syncytial endometritis', has been included in some series as a neoplasm (Ewing, 1910; Hertig and Sheldon, 1947), but there is no convincing evidence for this, and Novak and Seah (1954) do not consider the condition to be fatal. Although some cases may cause serious diagnostic difficulties, both clinically and histologically, the condition is best regarded as an abnormal persistence of placental site cells.

Although not encountered in this series, one other source of diagnostic difficulty should be considered, that of a further pregnancy occurring within a few weeks of a spontaneous or molar abortion. This may initially be detected as a rise in gonadotrophin excretion during follow up, but should a curettage be

performed it is important to remember that early trophoblast is histologically very similar to that of choriocarcinoma (Hertig and Mansell, 1956; Gore and Hertig, 1967; Elston, 1970).

In conclusion, this study has shown that a positive histological diagnosis of choriocarcinoma from uterine curettings is only possible in a limited number of cases. In most patients the correct management depends not only on the histological findings but also on a full consideration of clinical, hormonal, and radiological factors.

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