The clinical value of imaging with antibody to human chorionic gonadotrophin in the detection of residual choriocarcinoma

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Summary Choriocarcinoma can be imaged by external scintigraphy after intravenous administration of radiolabelled antibody directed against human chorionic gonadotrophin (HCG). The purpose of this study was to investigate whether antibody imaging was sufficiently sensitive and specific to improve the selection of patients for surgical resection of localised deposits of drug resistant or recurrent choriocarcinoma. Eighteen patients with raised serum HCG concentrations in whom the site of tumour was not known were investigated by antibody imaging and conventional imaging methods. When the tumour appeared localised, resection was attempted. Tumour was found at all sites in which both antibody imaging and conventional imaging methods were positive. Antibody imaging gave false positive results in 2 of 18 patients and false negatives in 5. Computerised tomography was false positive in one case and false negative in 2. In these patients, antibody imaging gave true negative and true positive results respectively. Of 8 patients with positive antibody imaging in whom resection was attempted, 5 achieved sustained complete response with up to five years follow up. It is concluded that antibody imaging is useful in selection of patients for surgery in drug resistant or recurrent choriocarcinoma.

Although the majority of patients with choriocarcinoma are curable with chemotherapy, drug resistant tumour is still the major cause of death (Begent & Bagshawe, 1982). Some of these patients have localised disease which can be cured by surgical resection, usually combined with adjuvant chemotherapy. Success of this strategy depends on accurate localisation of the tumour and on discrimination between viable tumour masses and the residual non-viable masses often found at sites from which choriocarcinoma has been eradicated. The presence of drug resistant choriocarcinoma is demonstrable by measurement of serum human chorionic gonadotrophin (HCG) concentrations. The sensitivity of this test exceeds that of any present imaging method so that patients with drug resistant choriocarcinoma are seen with rising serum HCG values but no clear indication of the site of active tumour.

Antibody imaging, in which tumours are imaged by external scintigraphy after intravenous injection of radiolabelled antibody directed against HCG provides a way of locating these tumours and demonstrating HCG production at the site concerned. Earlier studies of antibody imaging have shown that large deposits of choriocarcinoma can be located and that the sensitivity was sometimes sufficient to make the investigation useful in clinical decision making (Begent et al., 1980; Goldenberg et al., 1980, 1981).

This paper describes a study in which antibody imaging was performed in patients with drug resistant or recurrent choriocarcinoma in whom there was a rise in serum HCG values but the site of tumour was not known. The results were compared with those of conventional imaging methods and assessed for their value in selection of patients for surgery.

Materials and methods

Antibodies

The details of the antibodies directed against HCG, their purification and radiolabelling have been described previously (Searle et al., 1984; Begent et al., 1980). Briefly, a mouse monoclonal (W14A) and a sheep antibody to HCG were purified by binding to a column of HCG linked to Sepharose CL 4B and eluted with ammonium thiocyanate. They were labelled with 131I-Jodine (131I) by the chloramine T method and aggregates removed by gel filtration.

Administration to patients

The thyroid was blocked with potassium iodide 60 mg tds for 10 days, starting 24 h before administration of antibody. Potassium perchlorate 200 mg 6 hourly was given 4 doses after antibody administration. One hundred to 500 µg antibody labelled with 0.6–1.6 mCi 131I was given i.v. after negative intradermal testing for immediate type hypersensitivity with 10 µg antibody.

Imaging

Background radioactivity in normal tissues was simulated by giving ⁹⁹ᵐ Tc sulphurcolloid (⁹⁹ᵐ Tc) labelled albumin and ⁹⁹ᵐ TcO₄⁻ 45 min before imaging. Images of ¹³¹I labelled antibody and ⁹⁹ᵐ Tc subtraction medium were obtained 24 h after antibody administration using a Nuclear Enterprises LFOV gamma camera linked to a Nodcrest computer. The ⁹⁹ᵐ Tc image was subtracted from that of ¹³¹I antibody to identify areas of specific antibody uptake as described by Goldenberg et al. (1978). Numerical analysis of areas of relative accumulation of ¹³¹I antibody on the subtraction image was performed by the method of Green et al. (1984). In brief, regions of interest were drawn around the suspect area and around an apparently normal area in the same organ or tissue. The ratio of counts of ¹³¹I in the two regions was compared with that of ⁹⁹ᵐ Tc in the same regions. The difference between the two ratios was expressed in terms of standard deviations known as an Fx value. Areas known to produce artefacts in subtraction imaging such as the urinary bladder, heart and lower border of the liver (Begent, 1985) were excluded from analysis.

Results

Eighteen patients with drug resistant or recurrent choriocarcinoma in whom the site of tumour was not known were studied. In nine patients the antibody was of sheep and in nine of mouse monoclonal origin. No difference was seen between the images with the two reagents. Numerical analysis of images was performed by the method of Green et al. (1984) in 12 of these. The remaining 6 patients were...
studied before this method was devised and the data were acquired in a form which was not analysable. The results of the numerical analysis are shown in Figure 1. Sites at which tumour was later found tended to have higher Fx values than other sites at which no tumour was found. If an Fx value of +4 or greater is considered positive this gives a predictive value of a positive:

\[
\frac{\text{True + ve}}{\text{True + ve + false + ve}} \times 100 = \frac{9}{11} \times 100 = 82\%
\]

![Fx in choriocarcinoma](image)

Figure 1 Numerical analysis of antibody imaging in patients with choriocarcinoma. Fx values are for sites which were suspect on visual examination of subtraction images and for apparently normal areas for each patient. A mean of 8.5 areas was studied in each patient. Results have been separated according to whether tumour was subsequently found at the indicated site.

The higher the Fx value, the greater was the probability that the result was a true positive. It should also be noted that 50% of tumour sites gave false negative results.

Interpretation of the earlier studies which could not be analysed by the Fx method was done subjectively using the experience gained from the Fx studies.

The results of antibody imaging were compared with the findings of computerised tomography (CT), ultrasound and subsequent surgery. The results are shown in Table I and indicate the value of antibody imaging in selection of patients for surgery. Serum HCG concentrations ranged from 18 to 358,096 iul⁻¹ (median 321). Antibody imaging was negative in the patient with a value of 18 iul⁻¹ but positive in 2 patients with values between 20 and 30 iul⁻¹. Although the value of 358,096 iul⁻¹ might have been expected to be associated with complexing of antibody to HCG in the circulation, this did not prevent tumour localisation.

After antibody imaging and other investigations 11 patients were judged suitable for surgical resection of tumour. Eight of these had positive antibody imaging at the site concerned. The other 3 were operated on when antibody imaging was negative because of positive CT or ultrasound.

The relationship of antibody imaging to the histological findings in the resected tissue is shown in Table II. Of the 3 patients who had negative antibody imaging viable tumour was found in 2 but only necrotic tissue in the third. Two of the patients who had tumour resected had positive antibody imaging when other investigations gave false negative results. The tumours were pulmonary and uterine respectively.

![Table I Antibody imaging and selection of patients with choriocarcinoma for surgery](image)

| Site        | True positive | False positive | False negative |
|-------------|---------------|----------------|----------------|
| Lung        | 6             | –              | 3              |
| Brain       | 2             | –              | –              |
| Pelvis      | 2             | –              | 2              |
| Other abdominal | 1 | 2 | – |

Antibody imaging gave true-positive results in two cases in which other methods produced false-negative results.

The value of surgery to such patients depends on whether they attain a sustained complete remission. Five of the eight patients with positive antibody imaging whose tumours were resected achieved this as shown in Table III. Figure 2 shows an example of antibody imaging in which the tumour was located and resected leading to complete response. Figure 3 shows the effect of resection of choriocarcinoma in another patient where all other means of imaging had failed to locate the tumour.

![Table II Comparison of antibody imaging and surgical findings in patients with choriocarcinoma](image)

| Site        | Resections | True positive | False positive | True negative | False negative |
|-------------|------------|---------------|----------------|---------------|----------------|
| Lung        | 9          | 6             | –              | 2             | 1              |
| Brain       | 1          | 1             | –              | –             | –              |
| Pelvis      | 1          | 1             | –              | –             | –              |

Antibody imaging gave true-positive results in two cases in which other methods produced false-negative results.

![Table III Effect of surgery in patients with choriocarcinoma with positive antibody imaging](image)

| Site        | Sustained complete response | Early relapse |
|-------------|----------------------------|---------------|
| Lung        | 5                          | 1             |
| Brain       | 0                          | 1             |
| Pelvis      | 0                          | 1             |

Discussion

Previous studies have shown that antibody imaging with antibody directed against HCG can locate deposits of choriocarcinoma (Begent et al., 1980; Goldenberg et al., 1980, 1981; Searle et al., 1984). This study shows that the method has a sensitivity and specificity which make it useful in clinical management.

The clinical situation chosen in which to try to locate tumour is a demanding one because measurements of serum HCG concentration give a very sensitive indication of the
presence of choriocarcinoma. The tumours resected from patients in this study often contained only microscopic areas of viable tumour. Necrotic areas are a characteristic feature of choriocarcinoma, particularly if chemotherapy has been given, and formed the greater part of several of the tumours excised. This explains why deposits of choriocarcinoma can sometimes be imaged by CT when serum HCG levels are only modestly raised. Since antibody imaging is presumed to depend on the presence of viable choriocarcinoma, it is remarkable that tumour could often be located by antibody imaging when serum HCG concentrations were less than 1,000 mIU/l and occasionally when they were below 100 mIU/l.

Nevertheless, antibody imaging needs to be reliable in patients with very small deposits of tumour if it is to indicate the site of viable tumour and whether an attempt at resection is reasonable. The finding that tumour could sometimes be located when CT and ultrasound failed and that patients subsequently benefitted from the resulting tumour resection shows that antibody imaging has a place in the management of drug resistant or recurrent choriocarcinoma.

The potential of antibody imaging for discriminating between viable and necrotic tumour is illustrated by one patient who had positive CT but negative antibody imaging. When resected, the lesion was found to contain only necrotic tissue. The use of antibody imaging in this role is limited by its sensitivity so that, in practice, it is not possible to tell whether negative antibody imaging with positive CT means that there is no viable tumour or merely that there is too little to be detected by antibody imaging. To a considerable extent antibody imaging and other imaging methods are complementary. All of the patients in this study who had positive antibody imaging and CT or ultrasound had viable tumour at the site concerned. When only one investigation was positive there were false positives and false negatives on each side.

Antibody imaging can be difficult to interpret, particularly when small tumours are being sought. The Fx method (Green et al., 1984) has done much to resolve this problem by providing an objective means of interpretation and giving the result in numerical terms so that the probability of a result being correct can be calculated.

There are other ways in which antibody imaging may be improved such as by use of 111-Indium labelled antibodies (Rainsbury et al., 1983; Fairweather et al., 1983; Buckley & Searle, 1984), 123-Iodine labelled antibodies F(ab) fragments (Mach et al., 1980; Buchegger et al., 1983; Chatal et al., 1984; Larson et al., 1983) and second antibody (Begent et al., 1982). These topics and the relative merits of monoclonal and polyclonal antibodies have been discussed previously (Begent, 1985). As antibody imaging develops so other imaging methods are also likely to advance and the selection of patients for surgery to improve further.

The proportion of patients with choriocarcinoma whose disease is not eradicated by chemotherapy is small but some of these can be cured by the additional use of surgery (Begent & Bagshawe, 1982). Antibody imaging makes a valuable contribution by enhancing our ability to locate viable tumour and improving selection for surgery.

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