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RADIOIMMUNODETECTION OF OVARIAN CANCER

KATRINE RIKLUND ÅHLSTRÖM, SVEN-OLA HIETALA, ULF STENDAHL and TORGNY STIGBRAND

Radioimmunoscintigraphy (RIS) is a potentially valuable method for the detection of primary, secondary and recurrent malignant tumours. Antigens that have been used for monitoring as well as for RIS of ovarian carcinomas include CA 125, PLAP, HMFG, and CA 19-9. Between 70 and 100% of the tumours have been detected at RIS when these antigens have been used. Conventional methods, e.g., computerized tomography (CT) and ultrasonography (US), demonstrate similar or lower detection rate than RIS for tumour diagnosis. RIS gives additional information to conventional radiological methods (CT and US) for the detection of occult ovarian carcinomas. A review of earlier investigations is given and our own recent results using PLAP as a target antigen are presented. The future potential of the technology is discussed.

The principle of radioimmunoscintigraphy (RIS) is based on the expression of tumour-related antigens on malignant cells. Several antigens have been tested as targets for radiolabelled monoclonal antibodies (MAb), for both detection and therapy of ovarian carcinomas. If the antigens are shed into the circulation, the changes in serum levels can be used to monitor the disease. Table 1 summarizes some recent markers used to monitor ovarian carcinomas.

Cancer antigen 125 (CA 125) is the most commonly used ovarian tumour marker (1). The serum level of this antigen is elevated in about 80% of the patients with ovarian carcinomas (Table 2), and the elevation might precede clinically detectable progression by several months (2). The antigenic determinants in CA 125 are associated with high molecular mass proteins (300 to 500 kDa) derived from the coelomic epithelium in the embryo and in the adult. However, the marker has not been detected in the normal foetal or adult ovary, although trace amounts have been found in several normal organs (3). Several different MAbs have been raised against antigen CA 125, and several assays are available. This marker reaches high serum levels in some benign conditions, such as pregnancy and disorders cuasing ascites (4). Placental alkaline phosphatase (PLAP) and the almost identical PLAP-like isozyme are other markers attracting attention as potential tools for RIS. They are most abundantly expressed in tumours derived from the testis or the ovary. Placental alkaline phosphatase (PLAP) has recently been shown to be the placental IgG receptor (5–7), enabling radiolabelled immunoglobulins to be bound to, and possibly to be internalized by the malignant cells expressing the antigen. Previously considered to be an enzyme, PLAP has the property to bind MAbs specifically as an antigen target, and non-specifically as a general IgG receptor. These features may explain the promise of some recent clinical trials using PLAP as target (Epenetos AA, personal communication), both for RIS and radioimmunotherapy (RIT). High levels of the antigen are normally expressed in the placenta, and eutopically, trace amounts are found in normal testis, lung, and thymus (8). Smoking is known to cause elevated serum levels (9). As a tumour marker for ovarian carcinomas, PLAP is elevated in approximately 50% to 60% of all epithelial ovarian carcinomas (Table 1).

Two other, less frequently used, ovarian cancer antigens are the human milk fat globulin (HMFG) (10), and cancer

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From the Departments of Diagnostic Radiology (K. Riklund-Åhlström, S.-O. Hietala), Medical Biochemistry and Biophysics (T. Stigbrand), and Gynaecologic Oncology (U. Stendahl), University of Umeå, Umeå, Sweden.
Correspondence to: Dr K. Riklund Åhlström, Department of Diagnostic Radiology, University of Umeä, S-901 87 Umeå, Sweden.
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Table 1

Serum markers clinically evaluated in monitoring ovarian carcinomas

Tumour marker	Abbreviation	Detection rate %	(n/nn)	Reference	Ref. No.
Oncofoetal antigens					
Alpha-foeto protein	AFP	57	(13/23)	Donaldson et al. 1980	(20)
Carcinoembryonic antigen	CEA	65	(15/23)	Donaldson et al. 1980	(20)
	CEA	23	(11/46)	Schwartz et al. 1987	(21)
Placental alkaline phosphatase	PLAP	34	(23/67)	McDicken et al. 1985	(22)
	PLAP	49	(64/130)	DeBroe and Pollet 1988	(23)
	PLAP	65	(169/262)	Fisken et al. 1989	(9)
	PLAP	25	(12/47)	Bast et al. 1991	(24)
Carbohydrate determinants					
Cancer antigen 15.3	CA 15.3	57	(27/47)	Bast et al. 1991	(24)
Cancer antigen 19.9	CA 19.9	24	(6/24)	Ricolleau et al. 1984	(25)
	CA 19.9	33	(17/54)	Schwartz et al. 1987	(21)
Ovarian cystadeno carcinoma-associated antigen	OCAA	68	(65/95)	Bhattacharya et al. 1979	(26)
Tumour associated globulin	TAG 72	49	(23/47)	Bast et al. 1991	(24)
Lipid associated sialic acid	LSA	71	(71/100)	Schwartz et al. 1987	(21)
Proteins					
Cancer antigen 125	CA 125	82	(83/101)	Bast et al. 1983, 1987	(2, 27)
	CA 125	73	(77/105)	Klug et al. 1984	(4)
	CA 125	100	(12/12)	Berek et al. 1986	(1)
	CA 125	76	(74/98)	Schwartz et al. 1987	(21)
	CA 125	73	(190/262)	Fisken et al. 1989	(9)
	CA 125	81	(25/31)	Massuger et al. 1990	(28)
	CA 125	91	(43/47)	Bast et al. 1991	(24)
Hormones					
Human chorionic gonadotropin	hCG	17	(4/23)	Donaldson et al. 1980	(20)

n Number of patients with elevated serum levels of tumour marker
nn Number of patients with known ovarian carcinomas

antigen 19-9 (CA 19-9) (11). The former is a high molecular weight glycoprotein found on the epithelial surface lining of the mammary duct, ovarian follicles and crypts of the gastrointestinal mucosa (10). Associated with mucinous carcinomas, CA 19-9 is known as a valuable tumour marker for pancreatic cancer (12), but it also shows elevated serum levels in other malignant diseases. The antigenic determinant is a carbohydrate antigen related to the Lewis-blood group antigens (13). In the present investigation PLAP was used in a study of 14 patients with ovarian carcinomas, who were evaluated using MAb H7 for RIS. This MAb has been shown to be efficient in experimental RIS and RIT (14, 15).

Material and Methods

Patients. Fourteen women (24–78 years old, mean 49.5 years), referred to the Department of Gynaecologic Oncology, University Hospital of Northern Sweden for ovarian carcinoma were included. Four stage III patients had poorly-to-moderately differentiated serous carcinomas, and two had poorly differentiated endometrial tumours. Four stage II–IV patients had poorly differentiated unclassified adenocarcinoma diagnosed by cytology. One stage I patient had a moderately differentiated mucinous tumour, one stage III patient had a poorly differentiated immature tumour, one stage IV patient had a poorly differentiated mesonephric tumour, and one stage III patient had a poorly differentiated squamous cell tumour. Six patients (Table 2, Nos 1, 4, 7, 8, 10 and 12) had undergone debulking surgery and had residual or recurrent tumours at RIS. Eight patients (Nos 2, 3, 5, 6, 9, 11, 13 and 14) had primary tumours at the time of RIS. All but five patients received chemotherapy during the period of study.

Monoclonal antibodies and radiolabelling. All patients recieved MAb H7, a mouse MAb raised against PLAP (16). The MAbs, purified by protien A chromatography (17), were labelled with ^{131}I using the chloramin-T method (18). The specific activity was approximately 65 MBq/mg MAb, and labelling efficiency was always higher than 80%.

Antibody adminstration. The uptake of free iodine in the thyroid was blocked by potassium iodide (ACO, Sweden) during the investigation. All patients received between 57

Table 2

Clinical, radiologic, and radioimmunoscintigraphic findings in patients with ovarian carcinoma

Pat. No.	Tumour status[1]	RIS		CT	US
		(abd)	(thorax)		
1 •	Uterus, Douglas pouch and omentum	–	nd	nd	–
2	Peritoneum, oment and pleura.	+	nd	+	+
3 ••	Paraaortic lymph nodes, left ovary (10 × 15)	–	–	+	+
4 • ••	Omentum (2 × 3), Douglas pouch pelvic (12 × 12)	+	–	+	+
5 ••	Liver	+	+	+	+
6	Peritoneum, omentum, left ovary (7 × 5), right ovary (5 × 3), surrounding uterus	+	+	+	+
7 •	Douglas pouch left pelvic wall	+	–	+	–
8 •	Retroperitoneally lymph nodes bilat (3 × 2)	+	–	+	+
9	Cerebrum, lung	+	+	+	+
10 •	Peritoneum, pelivs	+	–	+	+
11	Multiple in liver, pelvis, close to left kidney (diam. 3,5)	+	+	+	+
12 •	bilat ovaries, ascites	–	–	+	+
13	Right parametric area (4 × 4)	+	+	+	nd
14 ••	Bilat ovaries, surrounding unterus oment, peritoneal carcinosis	+	–	+	+

[1] Tumour status includes locations and tumour size in cm.
• Hysterectomy and bilateral salpingoophorectomy before RIS.
•• Hysterectomy and bilateral salpingoophorectomy or second lood surgery after RIS.
+ Tumour seen
– Tumour not seen
nd Examination not done

and 100 MBq radiolabelled MAb i.v. No adverse effects were observed.

Scintigraphy. Scintigraphy was done with a General Electric 400T gamma camera connected to a PDP-11/34 computer system (DEC, USA) with a gamma-11 nuclear medicine software package. The patients were examined 7 to 16 days after injection of radiolabelled MAb. Anterior views of the chest and the abdomen were recorded. The acquisition time was always 30 min in each position. The bladder was catheterized before each examination.

Clinical, radiologic and histopathologic examinations. All but one of the patients were examined by CT (Somatom, Siemens), and 11 patients were examined by ultrasound (Acuson), with a maximum of two weeks time span to RIS. Histologic or cytologic examination of the tumours was done in all patients.

Results

Among the 14 patients with ovarian carcinoma lesions, RIS gave positive results in 11 (79%). The findings with RIS, CT, US, and clinical examination are summarized in Table 2. There were no false positive results. The smallest tumour visualized by scintigraphy had a diameter of 3.5 cm and was located close to the left kidney. However, the following case history illustrates the typical scintigraphic appearance of an advanced ovarian carcinoma. Patient No. 2 was a 52-year-old woman with a stage IV moderately differentiated adenocarcinoma of the ovary. The diagnosis was made just prior to RIS. Tumour growth had spread from the ovary to the peritomeum and omentum. RIS 7 days after injection of labelled MAb, demonstrated intense activity extending from the pelvis to the lower part of the abdomen (Fig. 1). CT was done 3 days later, and Fig. 2 shows a scan through the lower part of the pelvis, visualizing a large, irregular tumour with varying attenuation, indicating necrotic areas.

Discussion

Our results for the detection rate of RIS (Table 3) are apparently in accordance with previous investigations (70–100%). Some of the target antigens are known not to be expressed in all ovarian carcinomas, which might explain that the detection rate was less than 100%. Immunohistochemical examinations of paraffin-embedded sections of ovarian epithelian carcinomas show positive staining for PLAP in up to 67% of the cases (19). This is in agreement

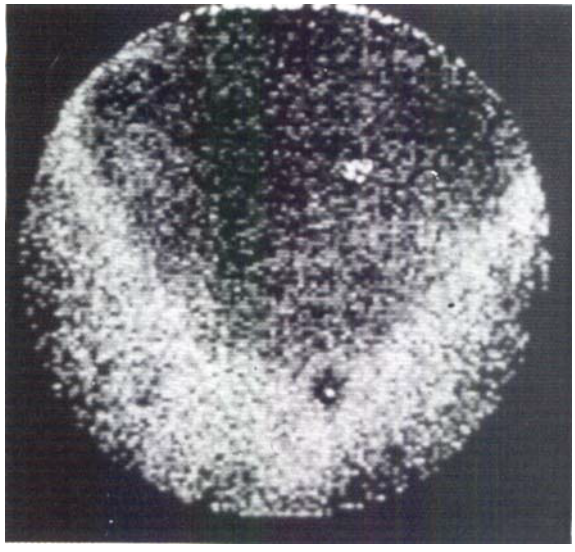

Fig. 1. RIS of a patient (No. 2) with a stage IV, moderately differentiated adenocarcinoma of the ovary. RIS was done 8 days after ilnjection of radiolabelled MAb. Extensive accumulation of MAb is seen in the lower part of the abdomen, and the pelvis. The upper white point indicates the umbilicus, and the lower white point indicates the symphysis.

with the results described above, and is also true for CA 125, expressed in approximately 80% of ovarian carcinomas (3). CA 125 has been used in several investigations (Table 3), to detect ovarian carcinomas with RIS. Several anti-PLAP MAbs have been used with RIS to demonstrate positive tumour immunolocalization in 60% to 100% (Table 3). Furthermore, HMFG has been used as an antigen in RIS, with positive results in 80% to 100% (Table 3). Despite the fact that only 25% of the patients with ovarian carcinomas had elevated serum levels of CA 19-9, positive findings with RIS are obtained in approximately 60% (Table 3). The relative accumulation of radiolabelled MAbs in humans is generally much lower than in experimental animals. When PLAP and MAb H7 were investigated in nude mice (14, 15) a tumour to non-tumour ratio of approximately 50 was found in comparison with a ratio of 2–3 in humans. This is partly due to the significant dilution effect in humans, with a body weight that averages 2 800 times more than that of mice, and significantly smaller relative tumour volumes. To further improve the diagnostic potential of RIS, tomographic imaging, such as that provided by single proton emission computerized tomography would be of singificant value. In comparison

Table 3

Clinical radioimmunoscintigraphy in patients with ovarian carcinomas

MAb	Antigen	Disease status	Detection rate (%)	(n/nn)	Radionuclide	Reference	Ref. No.
19-9(f)	CA 19-9	r	60	(3/5)	^{131}I	Chatal et al. 1987	(29)
H17E2(i)	PLAP	r	100	(6/6)	^{111}In	Malamitsi et al. 1988	(30)
H317(g)	PLAP	r	88	(7/8)	^{123}I	Critchley et al. 1986	(31)
H7(i)	PLAP	p + r	79	(11/14)	^{131}I	Riklund et al. 1991	(32)
HMFG2(i)	gp	p + r	89	(8/9)	^{123}I	Epentos et al. 1982	(33)
HMFG2(i)	gp	r	100	(1/1)	^{123}I	Epentos et al. 1985	(34)
HMFG2(i)	gp	p	95	(19/20)	^{123}I	Granowska et al. 1986	(35)
HMFG2(i)	gp	p + r	89	(16/18)	^{123}I	Pateisky et al. 1985	(36)
HMFG2(i)	gp	r	79	(15/19)	^{123}I	Pateisky et al. 1987	(37)
HMFG2(i)	gp	r	89	(8/9)	^{131}I	Pectasides et al. 1988	(38)
$NDOG_2$	PLAP	r	57	(4/6)	^{123}I	Davies et al. 1985a	(39)
$NDOG_2$	PLAP	p + r	73	(11/15)	^{123}I	Davies et al. 1985b	(40)
OC-125(f)	CA 125	r	67	(12/18)	^{131}I	Chatal et al. 1987	(29)
OC-125(f)	CA 125	r	88	(14/16)	^{111}In	Hunter et al. 1987	(41)
OC-125(i)	CA 125	r	87	(7/8)	^{111}In	Malamitsi et al. 1988	(30)
OC-125(f)	CA 125	r	84	(36/43)	^{131}I	Barzen et al. 1989	(42)
OV-TL 3(f)	OA 3(g.p)	p	94	(16/17)	^{111}In	Massuger et al. 1990	(43)
791T/36(i)	Tumour stroma	p + r	92	(11/12)	^{131}I	Symonds et al. 1985	(44)
791T/36(i)		p + r	98	(39/4)	^{131}I, ^{111}In	Powell et al. 1987	(45)

n Number of patients with elevated serum levels of tumour marker
nn Number of patients with known ovarian carcinomas
(i) Intact MAb
(f) MAb fragment, Fab or $F(ab')_2$
p Primary tumour
r Recurrent tumour
gp glycoprotein

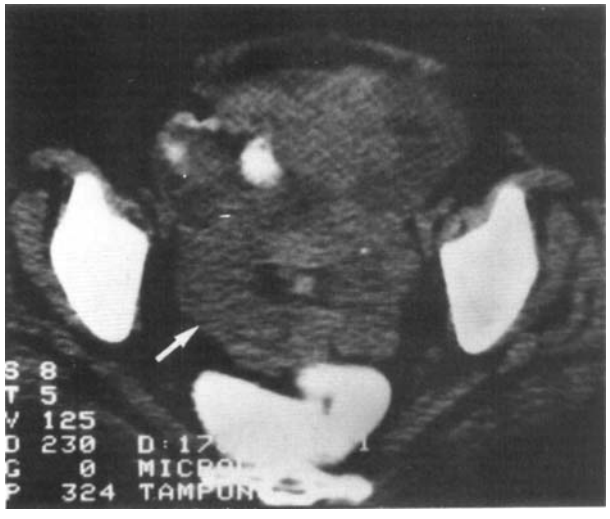

Fig. 2. CT scan through the lower part of the pelvis after peroral and i.v. contrast enhancement in the same patient as in Fig. 1. A large tumour (arrow) with necrotic areas is seen.

with CT and US, the sensitivity of RIS was similar or greater, but these techniques should be regarded as complementary rather than competitive. This is due to the fact that CT and US detect morphological changes in density in tissues, but have a poor discrimatory capacity when malignancy and posttreatment changes are sought, whereas RIS identifies viable tumours.

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