Clinical and Laboratory Data in Patients with S.L.E.-like Syndrome associated with Mitochondrial Antibodies

Case No.	Clinical Data	Duration of Illness (Weeks)	Date of Tests	Mitochondrial Antibodies (I.F.L.)	E.S.R. (mm in 1 h)	A.S.O. Titres	W.B.C. ($\times 10^9/l$)	% Neutrophils	% Band Forms	% Lymphocytes	% Monocytes	% Eosinophils	% Basophils	IgG (g/l)	IgM (g/l)	IgA (g/l)	C3 (g/l)
1	Arthralgia, myalgia pleuritis, pericarditis	8	12/1/73 18/5/74	50 0	91 7	40 32	8.6 6.8	75 765	6 0	15 21	1 0	3 4	0 0	13.0	2.0	3.8	0.68
2	Pleuritis, pneumonitis, pericarditis	7	5/5/73 7/11/73	200 0	107 50	64 32	8.6 5.8	82 49	0 0	17 44	1 2	0 5	0 0	11.5	2.0	4.0	1.12
3	Myalgia, pleuritis, pericarditis	12	15/5/74 13/6/73	100 100	132 65	16 25	7.1 5.8	769 87	3 3	16 8	2 1	2 1	0 0	8.4 16.5	1.4 2.2	0.50 2.5	0.66 1.16
4	Pericarditis, pneumonitis	5	26/7/73 18/5/74	100 0	117 52	16 32	10 5.2	72 56	4 6	20 25	2 5	0 7	0 0	11.5 12.5	1.3 1.6	1.6 5.8	0.74 1.16
			4/3/72 5/5/72 20/7/72 1/6/74	200 200 100 0	117 52 8	16 32 16											

Conversion: SI to Traditional Units—W.B.C.: $1 \times 10^9/l = 1000/mm^3$. Immunoglobulins: 1 g/l = 100 mg/100 ml.

5-12 weeks—the normal serum immunoglobulin and complement levels, and the absence of L.E. cells and A.N.A. Mitochondrial antibodies occur in 5-8% of patients with collagen disorders though not as a rule in typical S.L.E. Some patients with mitochondrial antibodies who were studied had subclinical liver disease with raised alkaline phosphatase levels and periportal lymphoid cell infiltrates on liver biopsy (Walker *et al.*, 1970; Whaley *et al.*, 1970). Others presented with a chronic neurological disorder resembling multiple sclerosis (Fulford *et al.*, 1972). A larger series with a clinical picture suggestive of S.L.E. with mitochondrial antibodies was reported by Maas and Schuboth (1972) and a similar syndrome was observed by Berg *et al.* (1973). Most patients studied in Germany were women who suffered repeated attacks of fever, arthralgia, and pleural symptoms with a high E.S.R., absent A.N.A., and little evidence of subclinical liver disease. W.B.C. counts tended to be raised in the active phase but several patients had persistent lymphopenia. Mitochondrial antibodies were of high titre—256-16 000—with a tendency to decrease during remissions.

Our four cases seemed to show a similar syndrome, but less severe and less persistent. The mitochondrial antibodies were of lower titres and the test results became negative on remission. The presence of these antibodies in the acute stage and their decrease thereafter suggest a relation with the illness. The I.F.L.

could not be attributed to cardiolipin antibodies since tests for syphilis gave negative results (Catterall, 1972). The cause of this new S.L.E.-like syndrome, the stimulus to mitochondrial-antibody synthesis, and the long-term outcome of the disease are as yet unknown. It will be of interest to follow patients with repeated antibody tests to see if further clinical exacerbations are preceded by the reappearance of the antibodies, as occurs in the case of DNA-antibodies in classical S.L.E.

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PRELIMINARY COMMUNICATION

Ultrasound Monitoring of Hepatic Metastases during Chemotherapy

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Summary

Grey-scale ultrasonography has been found to be the most sensitive method of detecting metastatic disease of

the liver. In two cases the results of chemotherapy were monitored by ultrasound; the response to treatment could be distinguished from non-response and ultrasonography gave useful information when chemotherapy made radioisotope examination unreliable.

Introduction

The use of chemotherapy for patients with hepatic metastases requires a simple method for monitoring the response. The results of radioisotope methods (scintigraphy) are disappointing since the resolution is poor and uptake of isotope depends on phagocytic function, which may be impaired by chemotherapy. Radiological methods require repeated vascular intrusion, which is especially hazardous in patients suffering from hemostatic defects resulting from thrombocytopenia or extensive liver disease.

Grey-scale ultrasonography offers a simple non-intrusive means of visualizing the normal liver parenchyma and detecting small metastatic deposits which replace the normal anatomy (Taylor and Carpenter, 1974). Serial examinations during

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chemotherapy enable the response of the metastases to treatment to be assessed. A schematic diagram of the area scanned ultrasonically is shown in fig. 1. We report here two cases of hepatic metastases in which response and failure to respond to chemotherapy were monitored by ultrasound.

FIG. 1—Schematic diagram of parasagittal section through liver of supine patient showing liver (H) limited by diaphragm (D) above and inferior vena cava (IVC) posteriorly opening into right atrium (RA). Transducer (T) is moved through arc to produce simple sector scan.

Case 1

A 31-year-old man presented with progressive dyspnoea of five weeks duration, several small haemoptyses, anorexia, and weight loss. Physical examination showed a hard nodule in the right testis, a small hard node in the left supraclavicular fossa, and a mass of para-aortic nodes palpable in the abdomen. The liver was palpable 6 cm below the costal margin but the consistency was clinically normal. A liver scintigram showed multiple ill-defined cold areas at the porta and throughout the right lobe. An ultrasonogram showed that the normal liver structure had been replaced by homogeneous tumour material (fig. 2a). The serum bilirubin was raised at $46.2 \mu\text{mol/l}$ (2.7 mg/100 ml), serum alanine aminotransferase (SGPT) was raised at 70 IU/l (normal $<33 \text{ IU/l}$), while α -fetoprotein was absent. A chest x-ray picture showed multiple pulmonary metastases and mediastinal glandular enlargement. Owing to his lung condition lymphography was not performed. The presumptive diagnosis of teratoma of the testis was later confirmed at orchidectomy.

FIG. 2—B-mode ultrasonograms of liver. Parasagittal sections taken 2 cm to right of midline showing (a) 14/12/73 extensive replacement of normal liver structure with homogeneous tumour (T), which appears blacker. (Inferior vena cava can be seen posteriorly (V).) (b) 19/1/74, after chemotherapy, more normal structure with highly reflective areas consistent with fibrosis (arrowed); (c) 4/3/74, reappearance of homogeneous tumour in liver (T) and further homogeneous mass below liver due to enlarged para aortic lymph nodes (LN); (d) 3/4/74, after radiotherapy to liver and lymph nodes, disappearance of paravertebral nodal mass and liver size and consistency are normal except for areas of high-level echoes consistent with fibrosis.

Combination chemotherapy (vinblastine, actinomycin D, and methotrexate) was given immediately and was repeated a week later (McElwain and Peckham, 1974). This treatment was repeated after five weeks and after two months. One month after the start of treatment there was a definite improvement in his general health and appetite. Ultrasonic examination showed that the homogeneous tumour areas had been replaced by normal liver structure with more highly reflective areas seen in fibrotic processes (fig. 2b). A repeat liver scintigram showed fewer cold areas than had been noted before. Serum bilirubin and SGPT had returned to normal but alkaline phosphatase was slightly raised at 125 IU/l (normal $25-92 \text{ IU/l}$). His cough stopped and the pulmonary lesions were reduced in size. Right radical orchidectomy was performed at this time. After two months the liver was impalpable and the chest x-ray picture showed nothing abnormal.

Three months after his initial treatment he deteriorated clinically and the liver became enlarged. The liver scintigram was unchanged and the liver function values were normal, but a repeat ultrasonogram showed that the liver structure was again replaced by tumour material, and there was a highly homogeneous mass below the liver which indicated the presence of enlarged para-aortic nodes (fig. 2c). This was confirmed by lymphography. It was decided to treat the liver and lymph nodes in the para-aortic and pelvic areas with radiotherapy. A total dose of 3000 rads was given to the liver over 29 days and 4500 rads to the para-aortic nodes over 45 days using a 6-MeV linear accelerator. After this treatment he was clinically very well and the liver and lymph nodes became impalpable. This improvement was reflected in the ultrasonogram which showed that the liver structure had returned to normal (fig. 2d). Repeat liver scintigraphy was not possible owing to inhibition of phagocytic activity by radiotherapy. subsequent repeat ultrasonograms showed no change and he remained well without evidence of liver metastases. Choroidal metastases later developed, however, but were successfully treated.

Case 2

A 59-year-old company director complained of a cough with white sputum of six weeks duration but otherwise felt well. A course of antibiotics had not improved his symptoms. A chest x-ray examination showed a prominent hilum on the right, and bronchoscopy showed a narrowing of the right upper lobe bronchus near its origin. Biopsy of this area showed only mucosal inflammatory changes. On cytological examination the sputum contained abnormal cells with the appearance of small-cell ("oat cell") carcinoma. The liver was palpable 2 cm below the costal margin, but this was not considered to be clinically enlarged. A $^{99\text{m}}\text{Tc}$ -sulphur colloid scintigram showed some enlargement of the liver with patchy uptake of the isotope but no definite cold areas. An ultrasonogram at that time showed definite homogeneous areas in the liver substance some 2 cm in diameter, and

FIG. 3—B-mode ultrasonograms of liver. Sagittal sections showing (a) 28/9/73 small relatively homogeneous mass replacing normal liver structure (dotted line); (b) 4/12/74 mass doubled in size and further metastasis (M) below it despite chemotherapy; (c) 9/1/74 marked growth of tumour and coalescence with lower metastasis and little evidence of high-level echoes seen in successful treatment; (d) 6/2/74 further growth of tumour and of overall liver size.

one of these is clearly shown in fig. 3a. Serum bilirubin and SGPT levels were normal and alkaline phosphatase was only slightly raised at 125 IU/l. No further evidence of metastatic disease was obtained from a brain scan, bone scan, or bone marrow biopsy. Combination chemotherapy was administered monthly consisting of cyclophosphamide 1 g, vincristine 1.5 mg, and methotrexate 200 mg, the latter infused over 48 hours, and was followed by a course of folinic acid. His cough was relieved by treatment and chest x-ray pictures showed no detectable increase in the small right-sided hilar shadow over a three-month period. After three months the liver had become palpably enlarged but liver function test results were normal. An ultrasonogram at the same parasagittal level as before (fig. 3b) showed that the metastasis had doubled in size and that the overall size of the liver had increased. Repeat ultrasonograms four and five months after the start of chemotherapy (figs. 3c and d) showed a progressive increase in the tumour size until most of the liver substance was replaced and gross hepatomegaly was apparent. Enlarging cold areas were now apparent in serial liver scintigrams. Six courses of chemotherapy were given, during which time there was a gradual decline in the patient's health. The liver continued to enlarge, right hypochondrial pain occurred, and the patient lost weight and developed spinal metastases. He died seven and a half months after the start of treatment, but permission for necropsy was refused.

Discussion

The ability to detect early metastases in liver has important implications for the surgeon considering a radical excision of malignancy as well as for the doctor considering the use of radiotherapy or chemotherapy. Physical examination is a time-honoured method of attempting to assess metastasis in the liver but, as shown by our second case, this may be extensive before any clinical enlargement is apparent. Liver function test results were significantly abnormal only when gross disease was present.

In Case 2 the use of ultrasound allowed us to measure precisely the size of the lesion as well as the overall size of the liver, estimated from the distance between the superior and inferior borders. Liver volume can be estimated by ultrasound by integrating multiple cross-sectional areas (Rasmussen, 1973),

but since this requires a computer it is simpler to assess liver size by the method mentioned above.

In case 1 both ultrasound and scintigraphy allowed detection of metastases before they were clinically apparent, but a formal comparison of the methods has shown that ultrasound is more reliable in the detection of early lesions (Taylor *et al.*, 1974). Moreover, it is more reliable than scintigraphy for monitoring the response of the lesion to radiotherapy (Taylor, 1974). Spurious cold areas may be seen on scintigrams after such treatment since local phagocytic activity of Kupffer cells, on which isotope uptake depends, is depressed.

Fine structure of liver cannot be displayed with most commercially available ultrasound scanners, which are suited only to urogenital and obstetric investigations. The scanner we used was developed on the principles used by Kossoff (1972) for detailed obstetric examinations, and its application to cancer diagnosis allows detection of hepatic lesions of less than 1 cm in diameter (Taylor *et al.*, 1973). Taylor *et al.* (1973) also described dramatic changes in the appearance of tumours after radiotherapy, and similar changes occurred after chemotherapy. Successful treatment in case 1 resulted in a change from a black homogeneous tumor area to more highly reflective areas with normal liver architecture. Unsuccessful treatment, as in case 2, was indicated by both the continued growth of the metastasis and the absence of any change in consistency.

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MEDICAL MEMORANDA

Usefulness of ^{99m}Tc-Technetium Pertechnetate in Periarthritis Nodosa

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Radioisotopes have a wide range of applications in the clinical investigation of many organs. Muscle diseases are an exception in this expanding field. We report here a case of periarthritis nodosa in which unusual scintigraphic images were obtained with ^{99m}Tc-pertechnetate. The kinetics of this isotope and the scintigraphic changes were followed during treatment and found to be useful clinical tools.

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Case Report

A 58-year-old butcher was admitted to hospital because of fever of unknown origin. The illness had started 10 days previously and had become progressively more severe. It was characterized by bouts of fever, generalized muscle ache, profuse sweating, and headache. The muscle aches were severe and more or less migratory though the musculi sternocleidomastoidii, masseteri, quadriceps femori, and solei were the most affected. There were few other symptoms and none which could suggest infection and the patient had taken no drugs before the onset of symptoms.

Three years previously an artificial anus had been constructed after a 60-cm colectomy performed for a glandular epithelioma. At that time and during follow-up the prognosis was considered good.

On admission the patient was fully conscious and did not look ill. The physical examination showed only a slight degree of pyrexia and extremely tender muscles. There was a discreet motor deficiency of the muscles of the thighs but no other neuromuscular abnormality.

Many clinical investigations were carried out. Bacterial, viral, and parasitic infections were ruled out using cultures of blood, urine, sputum, and faeces on various media as well as antibody characterization. The results of classical rheumatic tests were normal as were the creatine phosphokinase and aldolase serum levels. There was no anaemia but the W.B.C. was 20,700/mm³ with 94% granulocytes. The erythrocyte sedimentation rate (E.S.R.) was 75 mm in 1 hr (Westergren) and reached 125 mm in 1 hr three days later. The fibrinogen was 1,380 mg/100 ml