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LIVER BIOPSY IN METHOTREXATE TREATMENT

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Abstract. Fifty-seven liver biopsies were performed in 36 patients of whom 33 were psoriatics, on treatment or considered for treatment with methotrexate. Fifteen of the psoriatics were investigated prior to treatment; when comparing liver biopsies from these patients with biopsies from 23 treated psoriatics, no significant differences were found. A high incidence of pathological findings was observed in both groups. Patients with psoriatic erythroderma displayed the highest frequency of abnormal liver findings, 9 of 10 had increased fatty infiltration, and 8 of 10 showed signs of focal necrosis. These findings were not correlated with abuse of alcohol, obesity or methotrexate treatment. No cases of definite cirrhosis were observed. It is suggested that pathological liver biopsies in psoriatics may be related to the disease. Prolonged topical treatment or use of other drugs, however, could also contribute.

Nine patients had two biopsies done, 3 patients had three biopsies and 2 patients had four biopsies with an average interval of 10 months. These serial biopsies showed a tendency towards increased fatty changes. The results of the study do not suggest abandoning methotrexate as a treatment for severe psoriasis, but may stimulate a wider use of liver biopsy in the control.

Abnormality of liver function is a common complication in patients treated with methotrexate (2, 6, 7, 13, 14). Tests performed on serum, however, provide only limited insight into the state of the liver, and irreversible liver damage may develop despite normal results of liver function tests (12). Therefore, during the last 3 years we included liver biopsies in the system of control of patients on methotrexate. The present paper reports on the results of these biopsies.

MATERIAL AND METHOD

The investigations were carried out on 33 patients with psoriasis treated with or considered for treatment with methotrexate. Moreover, the study includes the results of biopsies on 2 patients with mycosis fungoides and 1 patient with pityriasis rubra pilaris on treatment with methotrexate. The patients were 18 men and 17 women, aged 26 to 78, and one 10-year-old oligophrenic boy with severe reactions which could not be managed by topical treatment. Sixteen of the patients (10 men and 6 women) were biopsied prior to treatment, while liver biopsies were performed in 26 (12 men, 13 women and one child) during treatment. Serial biopsies were made on 9 men and 5 women; of these, 2 patients had four biopsies, 3 had three biopsies, and 9 had two biopsies. The intervals between the biopsies were from 1 to 44 months, the average interval being 10 months.

The liver biopsies were obtained by the Menghini technique (11) using a 70×1.9 mm needle. Sections were cut 5 μ thick and stained with Haematoxin-Eosin, van Gieson, Prussian Blue, and Silver Nitrate. Microscopic examination of the biopsies was made by one of us without knowledge of the clinical data.

Fatty infiltration, periportal and parenchymatous inflammation, and focal necrosis were estimated in three degrees marked $+$ to $+++$. Where slight fatty infiltration, minor signs of inflammation or single areas with focal necrosis were observed, the sign $(+)$ has been used.

All patients on methotrexate followed the normal control procedure of the department. Serum glutamic pyruvate transaminase (SGPT), leukocyte count, thrombocyte count, and serum creatinine were examined before treatment. SGPT, leukocyte count, and thrombocyte count were re-examined 5 days after each administration of methotrexate. Within the last year, patients considered for treatment also had bromsulphalein retention registered.

Methotrexate was administered intramuscularly in weekly doses of 25 to 50 mg. When the disease was under control the dosage was reduced to an average of 10 mg. In a number of cases, the intervals between the injections were also lengthened, generally to 10 or 14 days. Occasionally, the treatment was interrupted for several months.

As a whole, patients with heavy alcohol consumption were not considered as candidates for treatment with methotrexate. However, 3 patients with heavy alcohol consumption (patients 22, 24, and 36 in Tables I, II,

Table I. *Findings in 15 patients with psoriasis and 1 patient with pityriasis rubra pilaris considered for methotrexate treatment*

Pat. no.	Sex	Age	Fatty infiltration	Inflammation		Necrosis	SGPT[b]	BSP[c] (%)
				Periport.	Parenchym.			
4	♀	61	−	+	−	−	0.5	8
5	♀	51	(+)	+	−	+	0.7	6
6	♂	23	++	(+)	−	−	0.9	
8	♂	50	(+)	−	(+)	(+)	0.9	
13	♀	70	(+)	+	−	−	0.6	
19	♂	54	(+)	−	(+)	−	0.6	
20	♂	57	−	−	(+)	(+)	1.3	7
22[a]	♂	28	(+)	−	−	−	1.1	6
24	♂	47	++	(+)	+	+	4.0	9
27	♀	64	(+)	(+)	−	−	0.9	5
28	♂	40	−	−	−	−	0.7	8
29	♀	73	+	−	−	−	1.1	4
31	♂	59	−	−	−	−	0.6	3
32	♂	60	+	−	−	−	0.4	
33	♀	27	−	−	−	−	0.2	2
36	♂	54	+	++	(+)	(+)	3.3	11

[a] Patient with pityriasis rubra pilaris.
[b] Normal upper limit is 1.5 units.
[c] Normal upper limit is 5 %.

and III) are included in this study. Their weekly alcohol intake exceeded one litre of strong liquor or equivalent amounts of wine or beer. Due to the results of our examination, one of these patients (no. 36) did not receive methotrexate, but was managed on topical treatment. The two other patients could not be controlled on topical treatment, and continued to receive methotrexate. Both patients, however, agreed upon reducing their alcohol intake.

RESULTS

The data prior to treatment are shown in Table I. Out of 15 psoriatics, 2 had a moderate fatty infiltration; one of these had a heavy alcohol consumption, the other was obese. In addition, 8 psoriatics had slight fatty infiltration. One of these patients was a heavy drinker, the others neither abused alcohol nor were greatly overweight. The patient with pityriasis rubra pilaris had slight fatty infiltration. This patient had an alcohol consumption of more than one litre alcohol per week. Mild periportal or parenchymatous inflammation was found in 11 of 15 psoriatics prior to treatment with methotrexate. Focal necrosis, though mild (Fig. 1), was found in 5 of 15 psoriatics before treatment. Table I includes results of preliminary BSP.

Liver biopsies in patients treated with methotrexate (Table II) did not differ from biopsies from untreated patients. One of 23 psoriatics displayed heavy fatty infiltration, while 5 had moderate fatty infiltration. Eight psoriatics had slight steatosis. The patient with heavy fatty infiltration (no. 11) also displayed focal necrosis (Fig. 2) and periportal inflammation. She did not abuse alcohol, nor was she overweight. Of the patients with moderate fatty infiltration, 2 were obese and one was a heavy drinker. A moderate periportal inflammation (Fig. 3) was found in 2 patients and mild periportal or parenchymatous inflammation in 11 of the 23 psoriatics. Mild focal necrosis was found in 8 treated psoriatics. Of 2 patients with mycosis fungoides treated with methotrexate, one showed mild steatosis and mild periportal inflammation, while the other had a normal liver biopsy. Again, the patient with pityriasis rubra pilaris displayed a mild steatosis; but this time the biopsy also showed some evidence of slight fibrosis. On account of this and because the patient's skin lesions had cleared, his treatment was discontinued.

Table II includes values of SGPT prior to treatment and the highest values observed during treatment. No correlation was found between

Table II. *Findings in 23 patients with psoriasis, 1 patient with pityriasis rubra pilaris, and 2 patients with mycosis fungoides during treatment with methotrexate*

SGPT are values before treatment compared with highest values observed during treatment. The normal upper limit is 1.5. Duration of therapy is in months since initiation of therapy

Pat. no	Sex	Age	Duration of treatment (months)	Fatty infiltration	Inflammation		Necrosis	SGPT	
					Periport.	Parenchym.		Before	Highest
1	♀	68	12	+	−	−	−	0.7	3.1
2	♀	74	43	+	−	−	−	0.9	1.7
3	♀♂	65	72	++	−	(+)	+	0.7	3.7
4	♀♂	61	6	(+)	(+)	−	−	0.5	1.2
6	♂	23	6	++	(+)	−	−	0.9	1.8
7	♀♂	48	28	(+)	+	(+)	(+)	0.8	5.0
8	♂	50	4	(+)	−	−	−	0.9	9.0
9	♂	62	36	+	+	−	−	0.6	3.9
10	♀♂	59	13	−	−	(−)	(+)	0.2	2.3
11	♀♂	61	42	+	++	−	+	0.3	2.6
12	♀♂	65	18	−	−	−	(+)	0.4	3.3
13	♀♂	70	12	+	++	−	−	0.5	4.1
14	♂	22	45	(+)	+	+	+	0.3	3.3
15	♂	28	38	−	−	−	−	0.3	2.5
16	♂	63	48	++	(+)	(+)	+	0.3	3.5
17	♀♂	35	44	−	+	−	−	0.5	6.3
18	♂	10	46	−	−	−	−	0.9	4.2
21[b]	♀♂	78	30	(+)	(+)	−	−	0.1	5.0
22[a]	♂	28	6	+	−	−	−	1.1	3.5
23	♂	30	25	−	−	−	−	0.9	1.6
24	♂	47	7	++	(+)	−	−	4.0	4.9
25[b]	♀♂	51	42	−	−	−	−	1.0	2.3
26	♂	59	44	−	−	−	−	0.4	1.6
30	♀♂	51	53	−	−	−	−	0.3	2.1
33	♀♂	61	10	++	−	(+)	(+)	0.5	1.5
35	♀	50	6	−	−	−	−	0.5	8.3

[a] Patient with pityriasis rubra pilaris.
[b] Patient with mycosis fungoides.

Table III. *Results of serial liver-biopsies in 13 patients with psoriasis and 1 patient with pityriasis rubra pilaris in treatment with methotrexate*

Pat. no	Sex	Age	Fatty infiltration				Necrosis			
			Biopsy 1	Biopsy 2	Biopsy 3	Biopsy 4	Biopsy 1	Biopsy 2	Biopsy 3	Biopsy 4
1	♀	68	+	(+)	(+)	+	−	−	−	−
4	♀	61	+	(+)			−	−		
6	♂	23	++	++			−	−		
7	♀♂	48	(+)	(+)	+		(+)	−	−	
8	♂	50	(+)	(+)			(+)	−		
11	♀♂	61	+	+++			−	+		
13	♀	70	(+)	+			−	−		
14	♂	22	−	(+)	−	−	−	(+)	+	−
15	♂	28	−	−	−		−	−	−	
16	♂	63	+	++			−	+		
22[a]	♂	28	(+)	+			−	−		
23	♂	30	−	−	−		−	−	−	
24	♂	47	++	++			+	−		
28	♂	40	−	−			−	−		

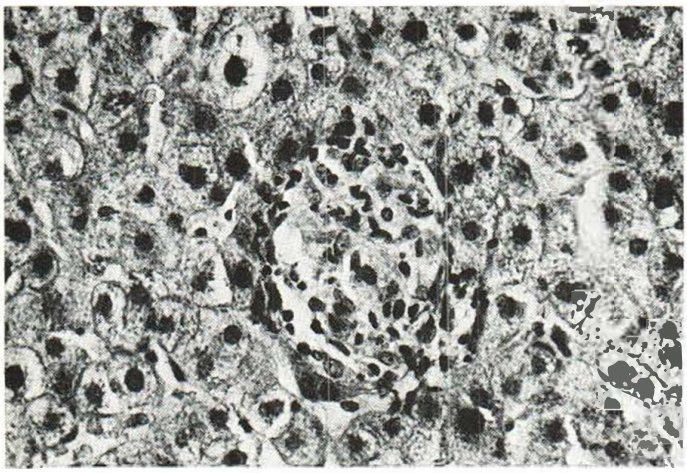

Fig. 1. Focal necrosis in liver biopsy from a 51-year-old female (Pat. 5) investigated prior to treatment with methotrexate. H and E stain, × 290.

increase in SGPT and pathological findings in the biopsies. One patient with one of the highest increases in SGPT during treatment (no. 35) showed no pathological findings in her liver biopsy. Fig. 4 shows the response of SGPT to methotrexate in this patient. All patients had an increase in SGPT during treatment. All but two had an increase in pathological values.

The results of the serial biopsies appear in Table III. They show a tendency towards an increase in steatosis. Fatty infiltration increased in 5 patients, remained at the same level in 8, and decreased in 1 patient. In 2 cases focal necrosis was found in the last but not in the first biopsy. However, in 3 cases focal necrosis could be demonstrated in the first, and not in the last biopsy. The serial biopsies showed no significant differences in periportal or parenchymatous inflammation. One patient, a 61-year-old female with severe pustular psoriasis and erythroderma had an increase in fatty infiltration besides an increase in periportal inflammation and in focal necrosis between her two liver biopsies. Also, in the second biopsy amyloidosis was found, probably due to her persistent pustulosis.

When comparing different groups of patients, only one group differed from the others by showing more severe results in the liver biopsies. Patients with psoriatic erythroderma, without regard to alcohol consumption or treatment, showed by far the largest number of pathological findings. Nine of 10 demonstrated mild to heavy fatty infiltration, and 8 of 10 showed scattered areas with focal necrosis. None of these patients had an alcohol intake of more than one litre strong liquor per week.

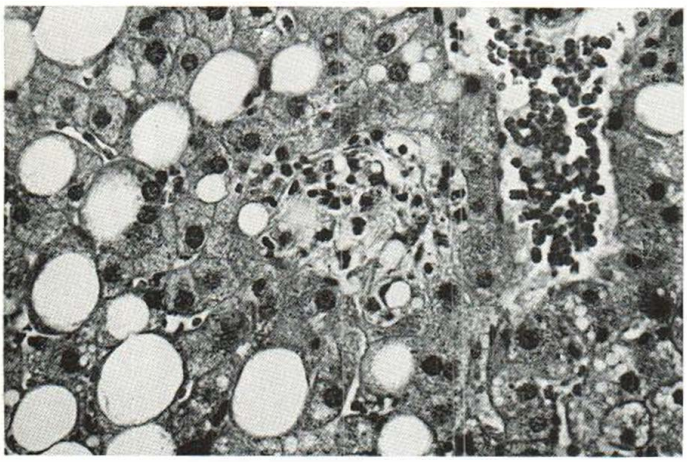

Fig. 2. Steatosis and focal necrosis in liver biopsy from a 61-year-old female (Pat. 11) 42 months after initiation of treatment with methotrexate. H and E stain, × 290.

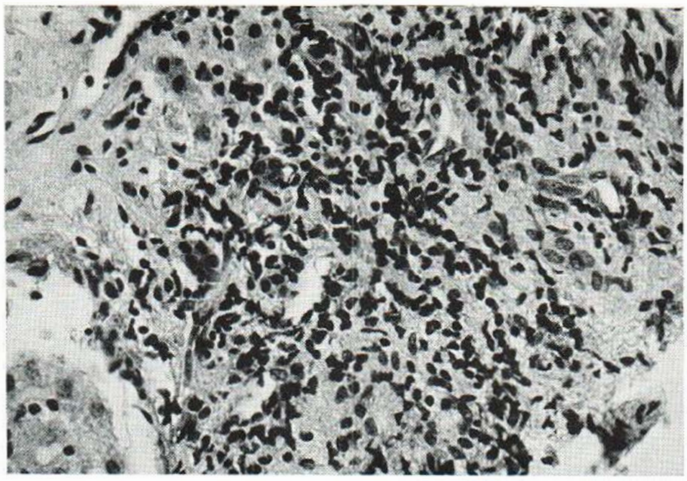

Fig. 3. Periportal inflammation found in liver biopsy from a 62-year-old male (Pat. 9) investigated 36 months after initiation of treatment with methotrexate. The micrograph shows many round cells. H and E stain, × 290.

DISCUSSION

Our findings of fatty changes of the liver in a large number of patients with psoriasis are in agreement with previous reports in the literature (1, 5, 9, 10). In a number of psoriatics, liver steatosis may be related to abuse of alcohol or obesity. However, in others no direct explanation for steatosis can be seen. Hepatic steatosis was not found in a higher degree in methotrexate-treated patients than in the group considered for methotrexate treatment. When excluding the two patients with mycosis fungoides and the patient with pityriasis rubra pilaris, the two groups are comparable. The severity of the disease and previous topical treatment were of the same character. The trend towards an increase in fatty infiltration found in serial biopsies may be a result of therapy. However, increase in age and duration of disease may be equally important matters to be considered.

Multifocal necrosis of the liver has previously been reported in psoriatics on methotrexate (3, 12), though this has not yet been investigated in a prospective study. Among our patients, focal necrosis was found with equal frequency in psoriatics on and without methotrexate. Therefore it is possible that this pathological finding together with periportal and parenchymatous inflammation may be related to the disease rather than to the methotrexate treatment. Other drugs may also have contributed to liver damage. Another possibility is that prolonged topical treatment may be livertoxic.

No cases of definite cirrhosis were observed in our study. Cirrhosis has previously been reported in leukaemic patients (4) and in psoriatics (3) treated with folic acid antagonists.

The results of SGPT confirm the large number of reports in the literature (2, 6, 7, 8, 12, 13, 14) on this sign of methotrexate hepatoxicity. In our study, all patients on methotrexate displayed an increase in SGPT, demonstrating this rise as an almost normal finding during methotrexate treatment. The lack of correlation between increase in SGPT and pathological liver biopsy demonstrates the limitation of these investigative procedures when performed alone. Although important in the control of patients on methotrexate. SGPT does not seem reliable in the evaluation of a hepatic toxicity of a slow, chronic nature. Further studies on serial liver biopsies seem

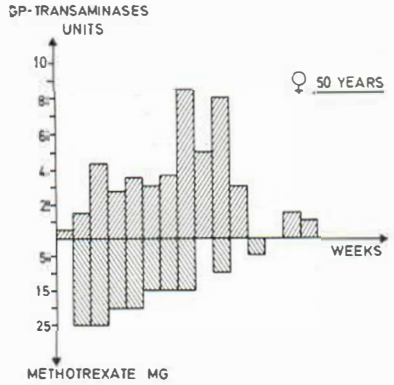

Fig. 4. Response of SGPT to treatment with methotrexate in a 50-year-old female (Pat. 35) suffering from psoriatic arthritis. Liver biopsy in this patient showed no pathological findings.

desirable. The observed high incidence of pathological liver biopsies in the present study indicates caution, but does not support the idea of abandoning methotrexate as an important drug in the treatment of severe psoriasis.

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