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CONCISE COMMUNICATIONS

Serious liver disease in a patient receiving methotrexate and leflunomide

We would like to present the first published report of serious liver disease in a patient receiving a combination of leflunomide and methotrexate (MTX) as therapy for active rheumatoid arthritis (RA).

The patient was enrolled in the first study of the combination of leflunomide and MTX (1). He enrolled in the study in April 1996. At that time, he was 51 years old and had a 4-year history of active seropositive RA. He was initially treated with nonsteroidal antiinflammatory drugs and 5 mg/day prednisone. In July 1992, he was started on MTX and eventually received a dosage of 15 mg/week with daily folic acid. He tolerated MTX without clinical or laboratory toxicity and without recurrent elevations in serum transaminase levels. He had no history of exposure to hepatotoxins and denied significant alcohol consumption, and there was no family history of liver disease. Despite these therapies, however, he continued to have active arthritis and was referred in April 1996 for enrollment in an open-label pilot study of the combination of MTX and leflunomide. Our institutional review board approved this study, and informed consent was obtained.

At his screening visit, the patient was receiving 15 mg/week MTX, 1 mg/day folic acid, 5 mg/day prednisone, calcium, and a multivitamin supplement with vitamin D. He had 30 painful and 18 swollen joints; physical examination results were otherwise unremarkable. He had a normal complete blood cell count, normal serum transaminase levels (aspartate aminotransferase 26 units/liter and alanine aminotransferase 38 units/liter), and an albumin level of 3.5 gm/dl, with negative hepatitis B and C serologies.

The patient received 100 mg leflunomide for 2 days, followed by reduction of the dosage to 10 mg/day. He did extremely well with this combination of MTX and leflunomide. He had significant improvement in his RA disease activity and by month 12 had no painful or swollen joints. Because of his response to this therapy, the leflunomide dosage was never increased to >10 mg/day. He had no clinical toxicity with this regimen. He did, however, have intermittent elevations of his serum transaminase levels (defined as elevations above the upper limit of normal for the test) during the first 18 months of therapy. He had 6 elevations over the course of 18 months (Table 1). Nine months after the initiation of therapy, his platelet count decreased (to $113 \times 10^3/mm^3$). This reduced platelet count persisted and ranged from $92 \times 10^3/mm^3$ to $133 \times 10^3/mm^3$. He received a higher dosage of folic acid (5 mg/day) followed by 10 mg/week leucovorin without improvement in the platelet count. Platelet antibodies were negative, and a liver and spleen scan obtained after 20 months of therapy showed mild enlargement of the liver and spleen. Colloidal uptake in the liver was normal, and the scan findings were interpreted as indicative of a hyperfunctioning spleen. Serum transaminase and albumin levels were normal at that time.

After the first 12 months of the combination, due to the patient's clinical response, the MTX dosage was reduced, and it was down to 5 mg/week by week 122. Despite the reduction in MTX dosage, his platelet count did not improve, although his RA disease activity remained under excellent control.

The study was completed at week 178, but the patient continued to receive 5 mg/week MTX and 10 mg/day leflunomide with daily folic acid for an additional 14 weeks. He underwent a repeat evaluation of his low platelet count. Abdominal ultrasound showed normal portal venous flow without evidence of portal hypertension, but splenomegaly was again noted. Computed tomography scan of the abdomen showed mild hepatomegaly at 15 cm with diffuse fatty infiltration and splenomegaly. Hepatitis A, B, and C serologies, antinuclear antibodies, serum iron studies, and ferritin level were all negative or normal. Results of synthetic liver function tests, including serum albumin, serum prothrombin time, serum alkaline phosphatase, and serum transaminases, were all normal. Liver biopsy showed diffuse marked fibrous septal formation with architectural distortions consistent with early micronodular cirrhosis and mild steatosis and nuclear variation without periseptal or lobular inflammation, which was assigned Roenigk grade IV. The patient received MTX for 7.5 years with a total cumulative dose of ~4.5 gm, and 10 mg/day leflunomide for 3.5 years with a total cumulative dose of 12.9 gm. MTX and leflunomide were discontinued.

This is the first reported case of serious liver disease (early cirrhosis) occurring in a patient receiving the combination of MTX and leflunomide. We are unable to state with any certainty whether the liver injury was due to either drug or to the combination. However, serious liver disease does occur with MTX, and liver enzyme elevations occur with leflunomide. We previously reported that reversible liver enzyme elevations occurred in 63% of patients receiving the combination of leflunomide and MTX (1). In that initial study, 3 patients were withdrawn due to persistent elevations in liver enzyme levels. Additionally, 3 patients underwent liver biopsies after 12 months of therapy, because they had recurrent elevations in liver enzyme blood tests and met the criteria for liver biopsy based on American College of Rheumatology guidelines for MTX monitoring (2). One liver biopsy was scored as grade I and 2 were scored as grade IIIA (mild fibrosis). It should be noted that after 12 additional months of therapy, none of these patients had repetitive elevations in liver enzymes, and repeat biopsies were not performed.

Both MTX and leflunomide have been associated with elevated liver enzyme levels. In the randomized study comparing MTX and leflunomide (3), serum transaminase elevations twice the upper limit of normal were noted in 9.3% of patients receiving MTX and in 11.0% of patients receiving leflunomide. One patient receiving leflunomide underwent a liver biopsy, which was reported not to show significant fibrosis.

It is noteworthy that this patient did not meet the published criteria for liver biopsy in the monitoring of patients receiving MTX (2), since there was never a sufficient number of transaminase elevations during the treatment period. In the first 12 months of treatment, 3 of 12 elevations in serum transaminase levels were just above the upper limit of normal. In year 2 of treatment, 4 of 12 such elevations were abnormal,

Table 1. Laboratory findings in a patient with serious liver disease who received methotrexate (MTX) and leflunomide*

Date	Week	AST, units/liter	ALT, units/liter	AP, units/liter	Albumin, gm/dl	Platelets, $\times 10^3$/mm^3	MTX dosage, mg/week	Leflunomide dosage, mg/day
4/22/1996	Screening visit	26	38	101	3.5	181	15	–
5/20/1996	2	29	34	113	3.6	182	15	10
6/3/1996	4	27	35	114	3.5	201	15	10
6/17/1996	6	26	26	112	3.7	188	15	10
7/1/1996	8	34	39	119	3.6	206	15	10
7/29/1996	12	27	42	119	3.6	170	15	10
8/26/1996	16	28	41	113	3.6	143	15	10
9/26/1996	20	33	**57**	111	3.4	150	15	10
10/31/1996	24	33	**52**	111	3.5	130	15	10
11/18/1996	28	30	35	109	3.5	155	15	10
12/16/1996	32	23	28	107	3.5	129	15	10
1/13/1997	36	28	35	112	3.6	113	15	10
2/10/1997	40	18	27	111	3.4	109	15	10
3/13/1997	44	**37**	**48**	116	3.6	127	15	10
4/7/1997	48	28	35	112	3.5	–	15	10
5/5/1997	52	33	38	106	3.6	105	15	10
6/16/1997	58	**39**	39	125	4.1	107	15	10
7/28/1997	64	**41**	41	119	3.6	113	15	10
9/8/1997	70	**45**	**54**	126	4.1	111	12.5	10
10/20/1997	76	27	37	117	4.0	98	10	10
12/1/1997	82	35	40	112	3.9	107	7.5	10
1/12/1998	88	29	32	112	3.9	–	7.5	10
2/23/1998	94	27	39	113	3.7	–	7.5	10
4/6/1998	100	28	32	107	3.9	103	7.5	10
5/18/1998	104	**51**	**54**	106	4.0	107	7.5	10
7/2/1998	110	35	**59**	105	3.9	111	7.5	10
8/17/1998	116	**42**	**52**	112	4.0	96	7.5	10
9/14/1998	122	32	34	111	4.1	114	5	10
10/26/1998	128	21	28	101	3.9	96	5	10
12/7/1998	134	30	40	105	4.1	111	5	10
2/1/1999	142	28	38	112	–	95	5	10
3/1/1999	146	39	48	103	4.5	107	5	10
5/3/1999	154	54†	**73**†	109	4.5	92	5	10
8/19/1999	168	16	23	121	4.4	109	5	10
11/9/1999	178	38	45	99	4.7	133	5	10
12/27/1999	184	21	30	112	4.4	112	5	10
2/28/2000	192	22	21	115	4.7	148	0	0

* AST = aspartate aminotransferase; ALT = alanine aminotransferase; AP = alkaline phosphatase. Normal values were as follows: AST 11–36 units/liter, ALT 6–43 units/liter, AP 36–110 units/liter, albumin 3.3–4.9 gm/dl, platelets 150–450 $\times 10^3$/mm^3. Bold numbers represent ALT or AST levels above the upper limit of normal for our laboratory.
† Normal values for both AST and ALT were 5–55 units/liter at an outside laboratory.

and there were only 3 elevations during year 3. It should be noted that there is only one prior report of a patient receiving MTX who developed serious liver disease and yet had completely normal liver enzyme levels over the course of several years of treatment (4). That patient, who had insulin-dependent diabetes, had a pretreatment biopsy showing Roenigk grade IIIA.

At this point, it is impossible to determine whether leflunomide (which can cause liver enzyme elevations) was a factor in the development of our patient's serious liver disease, whether the disease was due to MTX (which can cause serious liver disease), or whether the disease was due to a combination of both drugs. However, with increasing use of this combination in the management of RA, the rheumatology community should be aware of this finding and should report similar cases of serious liver disease through the FDA medical product reporting program MedWatch voluntary reporting system.

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Twins concordant for juvenile rheumatoid arthritis

Juvenile rheumatoid arthritis (JRA; now also known as juvenile idiopathic arthritis) is a heterogeneous group of disorders considered to be complex genetic traits. Associations and linkage between the HLA alleles and different subtypes of JRA have been described. The occurrence of disease in twins has been studied in adults with RA or ankylosing spondylitis. JRA occurring in affected sibpairs (ASPs) has been reported previously (1,2). However, reports of twins concordant for JRA are rare. Twins provide a unique opportunity to evaluate the role of genetics in a disease. Although twins are often exposed to the same environmental influences, co-occurrence of a polygenic disease such as JRA in both twins provides strong evidence for a genetic predisposition.

Of the 118 ASPs currently registered in the National Institute of Arthritis and Musculoskeletal and Skin Diseases–sponsored Research Registry for JRA ASP, 14 pairs are twins, both of whom have JRA. Abbreviated data on 7 of these twins were included in an earlier description of JRA ASPs (2). One of the 14 sets comprises a girl with polyarticular onset and disease course and a boy with pauciarticular onset and disease course. The remaining 13 sets are concordant for sex and are discussed further. Table 1 summarizes the clinical features of these 13 pairs and provides information on zygosity and HLA–DR typing on 11 sets from whom DNA is available.

All 13 pairs were concordant for onset (10 with pauciarticular onset, 3 with polyarticular onset) and course of JRA (8 with pauciarticular course and 5 with polyarticular course). Twelve sets were concordant for the presence or absence of antinuclear antibodies. The mean ± SD age at onset for all 26 affected twins was 3.9 ± 2.6 years. The first twins to develop symptoms of JRA did so a mean ± SD of 5.5 ± 6.7 months (range 0–24 months) before the second twins. Among the 104 nontwin ASPs in the registry, the mean ± SD difference in age at onset between the first and second sibling was 37 ± 35 months (range 1–132 months). The difference in age at onset for twins versus nontwins was statistically significant ($P = 0.002$

Table 1. Clinical, demographic, and HLA–DR data on the 13 sets of same-sex twins in the JRA ASP registry*

Twin pair/sex	Disease onsent	Disease course	ANA	Age at onset, years†	Difference in age at onset, years‡	Iritis	No. of diseased joints at onset	Zygosity	HLA–DR type
1/M	Pauci	Pauci	−	0.7	0.2		2	MZ	1, 16
	Pauci	Pauci	−	0.9			1		1, 16
2/F	Pauci	Pauci	+	2.1	0		1	MZ	11, 13
	Pauci	Pauci	+	2.1			1		11, 13
3/F	Pauci	Pauci	−	1.9	0		1	MZ	3, 13
	Pauci	Pauci	−	1.9			1		3, 13
4/F	Pauci	Poly	+	2.9	1		1	MZ	1, 7
	Pauci	Poly	+	1.9			2		1, 7
5/M	Pauci	Poly	−	4.7	0		2	MZ	7, 11
	Pauci	Poly	−	4.7			2		7, 11
6/F	Poly	Poly	+	5.5	0.6		22	MZ	1, 13
	Poly	Poly	−	6.1			14		1, 13
7/M	Pauci	Pauci	−	8.8	2	Yes	4	MZ	4, 7
	Pauci	Pauci	−	10.8		No	3		4, 7
8/M	Pauci	Pauci	−	1.3	0.2		1	MZ	1, 3
	Pauci	Pauci	−	1.5			1		1, 3
9/F	Pauci	Pauci	−	4.9	0.6		2	MZ	8, 9
	Pauci	Pauci	−	4.3			3		8, 9
10/F	Pauci	Pauci	−	1.4	0.4	No	2	MZ	13, 13
	Pauci	Pauci	−	1.8		Yes	2		13, 13
11/F	Poly	Poly	−	7.5	0		30	MZ	1, 3
	Poly	Poly	−	7.5			30		1, 3
12/F	Poly	Poly	−	4.0	0.3		14	NA	NA
	Poly	Poly	−	4.3			13		
13/F	Pauci	Pauci	−	3.2	0.7		2	NA	NA
	Pauci	Pauci	−	3.9			1		

* JRA = juvenile rhematoid arthritis; ASP = affected sibpair; ANA = antinuclear antibodies; pauci = pauciarticular; MZ = monozygotic; poly = polyarticular; NA = information not available.
† Mean ± SD age at onset among same-sex twins was 3.9 ± 2.6 years.
‡ Mean ± SD difference in age at onset among same-sex twins was 0.46 ± 0.56 years, or 5.5 ± 6.7 months.

by Student's *t*-test). The real time difference in disease onset among nontwin ASPs was a mean ± SD of 59 ± 52 months (range 0–270 months), while among same-sex twins the difference was a mean ± SD of only 5.5 ± 6.7 months ($P = 0.0004$ by Student's *t*-test). Two patients with pauciarticular JRA had iritis. Their cotwins had no history of iritis. HLA–DR typing results are summarized in Table 1. As a part of an ongoing genome-wide scan for JRA, more than 150 highly polymorphic, fluorescence-labeled microsatellite markers located on chromosomes 1–8 were analyzed to determine zygosity. All 11 sets of twins were identical at all markers analyzed, establishing monozygosity (Glass DN et al: unpublished observations).

In two studies of twins with adult RA, a significant increase in RA risk was found in monozygotic (MZ) versus dizygotic (DZ) twin pairs (3,4). Aho et al, in a population-based study of the Finnish Twin Cohort, identified 261 patients with a diagnosis of RA from among 4,137 MZ and 9,162 DZ same-sex twin pairs (3). In all, there were 9 MZ and 6 DZ twin pairs concordant for RA, and 2 patients among the DZ pairs had onset of RA at age 11. Their cotwins developed RA 9 years and 17 years later. The relative risk of RA was higher among MZ versus DZ twin pairs (8.6 versus 3.4). In a nationwide study from the UK, Silman et al identified 14 MZ and 4 DZ twin pairs who were concordant for disease (4). The concordance of 15.4% for MZ twins was significantly higher than the concordance of 3.6% for DZ twins.

In a series of 8 sets of MZ twins discordant for RA, 3 sets had had juvenile onset (5). The twin in 1 of the sets was seropositive, while in the other 2 sets the twin was seronegative with pauciarticular onset. In all 3 sets, the cotwin had not developed arthritis during 2–5 years of followup. Ansell et al described 11 twin pairs (5 MZ, 6 DZ) discordant for JRA (6). During 6–20 years of followup, 2 of the 5 MZ cotwins, but none of the 6 DZ cotwins, developed JRA or RA. One of the 2 MZ twin pairs concordant for arthritis consisted of 2 girls who had onset of arthritis within 11 months of each other; both later achieved remission of their disease. The other twin pair consisted of 2 boys who had onset of arthritis within 2 years of each other; each had disease that later progressed to ankylosing spondylitis. Baum and Fink reported on another set of female MZ twins concordant for JRA; these 2 patients had onset of seronegative erosive arthritis within 8 months of each other (7). Husby et al reported on a pair of MZ twins who were concordant for clinical features and iritis but discordant for the development of amyloidosis (8).

To our knowledge, the series reported here is the largest of twins concordant for JRA. Since the information is derived from a registry to which ASPs are selectively referred, we cannot draw conclusions about the frequency of JRA among MZ or DZ twins. To avoid selection bias, patients should ideally be ascertained from a population-based registry. However, the observation that same-sex twin pairs account for 11% of the total number of ASPs in the registry is noteworthy. In the United States, only about one-third of all twins are MZ (9). Among the 14 pairs of twins in the ASP registry, 11 pairs (78.6%) are MZ, 1 pair is DZ, and the zygosity of 2 pairs is yet to be determined. In RA, in which disease occurs in adulthood, it is conceivable that the twins may have different environmental exposures. In JRA, however, in which onset is in childhood or early adolescence, it is likely that both members of a set of twins are exposed to the same environment. The onset of disease in twins is much closer chronologically compared with that in nontwin ASPs. This suggests that genetically predisposed individuals exposed to appropriate genetic and/or environmental triggers are at high risk for JRA. It is likely that the disease phenotype is influenced by genetic factors, as demonstrated by the striking similarities in clinical features among the 2 twins in a pair.

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Possible association of "shrinking lung" and anti-Ro/SSA antibody

Although pulmonary involvement is observed in ~40% of patients with systemic lupus erythematosus (SLE), "shrinking lung" syndrome is a rare manifestation that is characterized by a reduction in volume of the lungs. Several such cases have been reported with SLE (1–5), and recently a case in association with primary Sjögren's syndrome (SS) was described for the first time (6). Here we report a case of shrinking lung complicated with anti-Ro/SSA antibody–positive SS and SLE and discuss a possible association between this syndrome and the autoantibody.

In January 2000, a 31-year-old woman was admitted to our hospital because of acute dyspnea, low-grade fever, and polyarthralgia. Five years earlier, she had been diagnosed as

Table 1. Patients with "shrinking lung" associated with anti-Ro/SSA antibody*

Report	Patient age/sex	Disease	Other evidence of disease activity	Autoantibodies				
				Ro/SSA	La/SSB	dsDNA	Sm	RNP
Munoz-Rodríguez et al (2)	24/F	SLE	Malar rash, lymphopenia	+	−	+	−	−
Kitamura and Okano (3)	56/F	SLE	Lymphopenia	+	−	+	−	−
Tavoni et al (6)	56/F	SS	Leukopenia, lymphadenopathy	+	+	ND	ND	ND
Present patient	31/F	SLE, SS	Lymphopenia, polyarthralgia, lymphadenopathy	+	−	+	−	−

* DsDNA = double-stranded DNA; SLE = systemic lupus erythematosus; SS = Sjögren's syndrome; ND = not described.

having SS because of sicca and the presence of anti-Ro/SSA. On the day of admission, she was febrile (38.4°C) and reported feeling dyspneic for several days. Physical examination showed small, swollen, tender lymph nodes in supraclavicular areas. Her respiratory sounds were attenuated in bilateral lower lung fields.

Laboratory examination showed lymphopenia (50 cells/mm^3) and depletion of complements (CH50 12.2 units/ml; normal 30–40). Antinuclear antibodies were positive with a homogeneous pattern, and both anti–double-stranded DNA and anti-Ro/SSA antibodies were present. Anti-La/SSB, anti-Sm, anti-RNP, and anticardiolipin antibodies were all absent. Urinalysis revealed neither proteinuria nor hematuria.

Chest radiographic study showed progressive elevation of the hemidiaphragms. Only sluggish movement of hemidiaphragms was observed by comparing maximal inspiratory and expiratory states. Arterial blood gas analysis yielded the following values: pH 7.479, P_{O_2} 51.1 mm Hg, and P_{CO_2} 31.5 mm Hg. Pulmonary function tests showed a restrictive pattern (inspiratory vital capacity 53.2%, forced expiratory volume in 1 second 78.7%, and diffusing capacity for carbon monoxide 42.8%). A diagnosis of SLE was made according to the 1982 revised criteria of the American College of Rheumatology (7), and coexistent shrinking lung syndrome was suspected. After administration of 50 mg of prednisolone, her symptoms disappeared and her lungs reexpanded normally.

The pathophysiology of this syndrome has not been well clarified, although several reports showed that it was attributable to diaphragmatic dysfunctions rather than to intrapulmonary disorders (8). While corticosteroids also improved the symptoms in previous cases (3,5), theophylline (4) and inhaled beta-agonist (2), which are effective for bronchial asthma, are also effective for this syndrome. This suggests that not only diaphragmatic dysfunctions, but also certain inflammations of bronchial walls might play a role in its pathogenesis.

We suggest a possible association between shrinking lung and anti-Ro/SSA, because anti-Ro/SSA was detected in our patient and in 3 previously reported SS or SLE patients who had the syndrome, as shown in Table 1 (2,3,6). Anti-Ro/SSA, which is rather specific for SS, can be detected in ~30% of SLE patients. This autoantibody has been reported to cause congenital heart block in infants (9) and correlates with lymphopenia (10). Lupus nephritis has been reported to correlate inversely with anti-La/SSB (10), which is related to anti-Ro/SSA. Concordantly, lymphopenia (or leukopenia) was present in all 4 patients listed in Table 1, and no renal manifestations were observed in these patients. Considering these findings, we propose the existence of a subtype of SLE with shrinking lung, lymphopenia, and anti-Ro/SSA positivity without nephropathy.

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