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CONCISE COMMUNICATIONS

Shrinking lung in primary Sjögren's syndrome

Primary Sjögren's syndrome (SS) is a condition of autoimmune exocrinopathy in which both T and B lymphocytes infiltrate and progressively destroy the salivary and lacrimal glands (1). Similar lymphocytic infiltrates may also invade the visceral organs, causing various extraglandular manifestations, including polyneuropathy and lung disease. Several pulmonary manifestations have been reported in primary SS, such as lymphocytic interstitial pneumonitis, interstitial pulmonary fibrosis, pleural disease, and lymphoproliferative disorders (2).

The shrinking lung syndrome is a pulmonary condition that may be linked either to a phrenic nerve neuropathy or to intrinsic diaphragm muscle weakness (3). It manifests in the form of small, clear lung fields without any evidence of interstitial or pleural disease, and is associated with a restrictive pattern on forced spirometry (3). It has been suggested that the condition may be due to a diaphragm dysfunction, but this hypothesis remains to be confirmed. Its association has been described in a few cases of systemic lupus erythematosus (SLE) (4–9), but not in any other autoimmune disease. We report herein the unusual case of a patient with primary SS and shrinking lung syndrome due to diaphragm dysfunction.

In February 1997, a 56-year-old woman, who had had dry eyes, xerostomia, arthralgias, and autoimmune thyroiditis since 1992 and who was being treated with L/T4 for hypothyroidism, developed bronchopneumonia in the right lower lung field. Chest radiographic examination showed an elevated diaphragm. Fiberoptic bronchoscopy with bronchoalveolar lavage and brushing excluded the presence of neoplasia, but showed the presence of a phlogistic infiltrate. Culturing of bronchoalveolar fluid samples did not reveal the presence of any infectious agent. Despite these negative findings, the patient was treated with antibiotics, steroids, and bronchodilator drugs, and a rapid resolution of the acute episode was seen.

Because of her sicca symptoms, however, the patient was referred to the Clinical Immunology and Rheumatic Disease Unit of the University of Pisa in November 1997. She presented with exertional dyspnea, and a chest radiograph showed clear, small lung fields and an elevated right diaphragm (Figure 1). A chest high-resolution computed axial tomography scan excluded the presence of mediastinal lymphadenopathy. The results of both a Schirmer's test and rose Bengal staining were consistent with keratoconjunctivitis sicca. A labial salivary gland biopsy showed the presence of lymphocytic infiltrates (a score of 4 according to the method of Chisholm and Mason) (10).

Blood tests demonstrated raised gamma globulin levels (2 gm/dl) and leukopenia (3,080 cells/mm^3). Antinuclear antibody was positive (with a diffuse pattern), and anti-Ro/SSA and anti-La/SSB antibodies were present. Cryoglobulins as well as anti–hepatitis C virus antibodies were absent. Muscle enzyme, erythrocyte sedimentation rate, blood urea nitrogen, serum creatinine, and electrolyte values were all within normal limits.

Pulmonary function tests showed a restrictive defect (medium degree). A study of maximal inspiratory pressure showed reduced values. Arterial blood gas levels were within normal limits. Electrophysiologic studies of the right supraspinatus and deltoid muscles demonstrated normal motor conduction velocities, and normal repetitive stimulation and quantitative electromyography results. In contrast, electroneurographic studies of the phrenic nerves, performed by stimulation in the neck at the posterior border of the sternomastoid muscles, showed significant bilateral motor neuropathy which was more severe on the right side.

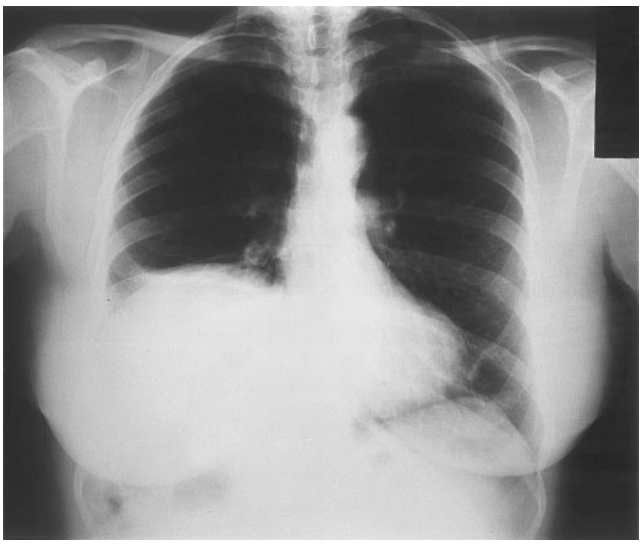

Figure 1. Posteroanterior chest radiograph demonstrating marked elevation of the right hemidiaphragm.

On the basis of these clinical, radiologic, electrophysiologic, histologic, and serologic features, a diagnosis of primary SS associated with a shrinking lung condition was made. Treatment with low-dose steroids, tear substitutes, theophylline, and inhaled β-agonist was started, and significant improvement in the clinical symptoms was seen. After >1 year of followup, the patient remains well and has not had any new episodes of bronchopneumonia.

This communication represents, to our knowledge, the first report of its kind to describe the occurrence of shrinking lung in a patient with primary SS. Our patient had had autoimmune thyroiditis and sicca syndrome for 5 years when she experienced an episode of bronchopneumonia. The diagnosis of shrinking lung was made based on a chest radiograph showing a clear, small lung field and an elevated right diaphragm, pulmonary function tests demonstrating a restrictive defect, and an electroneurographic study of the phrenic nerve showing significant motor neuropathy. The possibility that the diaphragm elevation might have been caused by myopathy linked to the patient's autoimmune thyroiditis could be excluded since her muscle enzyme, thyroid-stimulating hormone, and T4 serum levels were normal and electromyography of the right supraspinatus and deltoid muscles showed no abnormalities.

Among the systemic autoimmune diseases, the association with shrinking lung has been reported in SLE patients (4–9). The lung condition has been ascribed, in different cases, to phrenic nerve neuropathy, neuromuscular junction, and muscle involvement due to myositis, local vasculitis, and fibrosis (4). Phrenic nerve involvement, which is generally detected based on electrophysiologic studies, is one of the possible localizations of the mononeuritis multiplex that can sometimes develop during the course of SLE (11). In primary SS as well, mononeuritis multiplex linked to a vasa nervorum vasculitis has been described, involving the peripheral and cranial nerves (12,13). Phrenic nerve involvement leading to a shrinking lung syndrome has never been reported before in primary SS.

The most appropriate treatment for the shrinking lung syndrome remains unclear. Similar to the other systemic manifestations of connective tissue diseases, it seems to respond to corticosteroid therapy in some patients, although the optimal dosage has not yet been determined (14). Inhaled β-agonists have also been used with good results (15). Treatment with theophylline has been reported to be effective in the management of dyspnea in patients who develop shrinking lung syndrome during the course of SLE (3). In our patient with primary SS, we observed marked clinical improvement after combined treatment with low-dose steroids, theophylline, and inhaled β-agonist.

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Antiphospholipid antibodies in patients with Wegener's granulomatosis and polyarteritis nodosa

Antiphospholipid antibodies (aPL) have been associated with a spectrum of connective tissue diseases, especially systemic lupus erythematosus. The presence of these antibodies is associated with clinical events including venous and arterial thrombosis, miscarriage, and avascular necrosis. Antiphospholipid antibodies may also be seen in the setting of certain viral illnesses or medications, and in healthy individuals without clotting events (1,2). These antibodies have been noted in individuals with systemic vasculitis (3), but there is little information in the literature regarding the prevalence of aPL in Wegener's granulomatosis (WG) or polyarteritis nodosa (PAN) (3–10). We noted several patients with these vasculitides and aPL in our clinics, and undertook this study to define the prevalence and clinical significance of these antibodies in this group of patients.

Through the medical records department, we obtained the names of all inpatients with a discharge diagnosis of WG or PAN at Duke University Medical Center between January 1993 and June 1998. This starting date coincided with the introduction of standardized testing for aPL at our institution. Lupus anticoagulant (LAC), anticardiolipin antibodies (aCL), and anti–β_2-glycoprotein I (anti-β_2GPI) antibody assays were performed as described previously (11,12). LAC positivity was determined on the basis of the Russell viper venom assay, as described (11).

Review of the laboratory records revealed that 17 patients had been tested for aPL by their physicians. We also performed analysis for aCL in stored samples from an additional 32 patients, which had been used for other serologic testing (e.g., for rheumatoid factor). We then tested aPL-positive samples for the presence of anti-β_2GPI, which may correlate better than aPL with clinical events (13). Nine of 11 patients seropositive for aPL had stored sera from the date of the test. Results are summarized in Table 1.

Medical records of all patients tested were then sur-

Table 1. Patients' antiphospholipid antibody (aPL) status and clotting events*

Form of vasculitis	Antiphospholipid antibody status (dates ascertained)	Anti–β_2GPI antibody	Clotting event	Patient age at thrombosis	Duration of followup
PAN	aCL negative/LAC positive (6/98)	†	None	—	8 months
PAN	IgG aCL 16 (12/91)	Negative	None	—	47 months
PAN	IgM aCL 12 (6/92)	Negative	None	—	33 months
PAN	aCL negative/LAC positive (2/96)	Negative	None	—	8 months
WG	aCL negative/LAC positive (1/96)	Negative	None	—	34 months
WG	aCL negative (7/93, 9/93, 2/95, 10/95), LAC positive (7/93, 1/94), LAC negative (9/93, 2/95, 10/95)	Negative from 1994 sample	None	—	70 months
WG	LAC positive/IgG aCL 36 (6/94), LAC negative/IgG aCL 21 (3/97)	Negative from 1994 sample	None	—	51 months
WG	aCL negative/LAC positive (10/96)	Negative	None	—	1 month
WG	IgG aCL 19 (4/96)	Negative	None	—	36 months
WG	IgM aCL 14 (9/93)	Negative	Pulmonary embolus 12 years prior to vasculitis, myocardial infarction 6 years after onset of vasculitis	29 years	14 months
WG	aCL negative/LAC negative (4/94), IgM aCL 20 (8/97), aCL negative/ LAC negative (2/98)	†	Transient ischemic attack after starting hormone replacement therapy	46 years	57 months

* Anti–β_2GPI = anti–$\beta_2$glycoprotein I; PAN = polyarteritis nodosa; aCL = anticardiolipin antibody; LAC = lupus anticoagulant; WG = Wegener's granulomatosis. Values for IgG aCL: 1–15 units = normal; 16–40 units = low positive; 41–80 units = moderately positive; >80 units = highly positive. Values for IgM aCL: 1–10 units = normal; 11–20 units = low positive; 21–40 units = moderately positive; >40 units = highly positive. † Indicates that sera were unavailable from time of aPL testing.

veyed to confirm the diagnosis of vasculitis and to determine whether an aPL-associated clinical event had occurred. Recorded clinical events included deep vein thrombosis (DVT), pulmonary embolus, stroke, transient ischemic attack (TIA), myocardial infarction, miscarriage, and avascular necrosis. The presence of thrombocytopenia was not evaluated. Acquired risk factors for thrombosis were also recorded, including use of oral contraceptives or hormone replacement therapy, hypertension, diabetes, elevated lipids, tobacco abuse, and obesity (body mass index >27). Criteria for the diagnosis of vasculitis were entered into a database to analyze whether a specific feature of vasculitis correlated with the presence of aPL.

Twelve of the 13 patients diagnosed with PAN met American College of Rheumatology (ACR) criteria for this diagnosis (14). Thirty-three of 36 patients with WG met ACR criteria for this diagnosis (15). Three of the remaining patients were judged by 1 of the authors (NBA) as having WG. The final patient was diagnosed with PAN at an outside hospital and was not seen by the rheumatology service as part of her care at Duke University Medical Center.

Thirteen patients with PAN were tested for aPL (10 for aCL, 1 for LAC, 2 for both aCL and LAC). The sera from 4 patients (31%, Table 1) were positive. None of these patients had sustained an aPL-associated clinical event. One patient with PAN who was seronegative for aPL had had avascular necrosis of the hip at age 69.

Thirty-six patients with WG were tested for aPL (24 for aCL, 2 for LAC, 10 for both aCL and LAC). Seven (19%, Table 1) were seropositive. Two of these patients had sustained an aPL-associated clinical event. A 46-year-old woman with elevated IgM aCL had developed TIA shortly after starting hormone replacement therapy, but these had resolved after stopping medication. Another patient with elevated aCL had sustained a pulmonary embolus 12 years prior to onset of vasculitis, at age 29. He had also sustained a myocardial infarction 6 years after onset of WG. The remaining patients seropositive for aPL have not experienced clotting events for a mean of 32 months of followup (range 1–70 months, see Table 1).

Of the WG patients seronegative for aPL, 4 had had clinical events. A 19-year-old man had sustained lower extremity and subclavian vein thromboses along with splenic and renal infarctions all during the onset of his vasculitis. He had also sustained a second DVT 2 months later. A woman had sustained both DVT and pulmonary embolus at age 76, within 1 year of being diagnosed with WG. A 47-year-old man had sustained a DVT the same year he was diagnosed with WG. A woman with WG had had a miscarriage at 2 months of gestation.

In total, 2 of 11 patients with aPL and 5 of 33 without aPL had sustained a clinical event ($P = 0.65$ by Fisher's exact test). Nine of 11 patients with aPL had stored sera (from the time of aPL testing) available for anti–β_2GPI antibody assay. All patients were seronegative (see Table 1). Acquired risk factors for thrombosis were no more common in the group of patients with clotting events (mean of 1.3 versus 1.2 risk factors for those with versus those without thromboses, respectively).

Criteria for the diagnosis of WG and PAN were entered into a database for each patient, along with results of testing for antineutrophil cytoplasmic antibodies (ANCA). Fisher's exact test showed no statistical correlation between the presence of aPL and clinical features of vasculitis, including the presence of ANCA.

We add to the literature an additional experience from a group of patients with WG and PAN. Anticardiolipin antibodies were commonly observed in sera from our patients with

WG and PAN, but there was no statistically significant association between the presence of these antibodies and aPL-associated clinical events. In general, aCL were present in low titer, and repeat testing in some cases showed resolution of the antibody (see Table 1).

Anticardiolipin antibodies may occur as part of the hypergammaglobulinemia seen in vasculitis, or as the result of nonspecific binding in the assay for aCL (10). Alternatively, antigen exposed on the endothelium due to vascular injury may lead to aPL production. One would expect that if these antibodies are epiphenomenal rather than pathogenic, then anti–β_2GPI should be absent from this group of patients (13). We confirmed this by testing 9 patients from whom we had stored sera. All were seronegative for anti–β_2GPI. We caution that several patients were seropositive for LAC, which may correlate better with antibodies other than anti–β_2GPI.

Our study did not show why patients with vasculitis develop thrombosis. We did not test for common causes of thrombosis (such as factor V Leiden). Acquired risk factors for thrombosis were not more common among patients who sustained thrombotic events. Exposure of the endothelium during the vasculitic process may render the endothelial surface more thrombogenic. Defective release of stored vascular tissue plasminogen activator was seen in a small group of patients with systemic vasculitis (16).

Based on our experience, we would not recommend routine screening of patients with WG and PAN for aPL. If a patient with vasculitis has a thrombotic event, aPL may play a role. Further testing for anti–β_2GPI or serial testing to determine whether the aPL persists may be helpful in clarifying the role of these antibodies for a given patient with thrombosis, prior to committing the patient to long-term, high-intensity anticoagulation therapy.

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Long-term followup of naproxen-induced pseudoporphyria in juvenile rheumatoid arthritis

Naproxen is the most commonly used first-line agent in the treatment of juvenile rheumatoid arthritis (JRA) (1). It is a member of the phenylpropionic acid–derivative group of nonsteroidal antiinflammatory drugs (NSAIDs), which are known to cause pseudoporphyria, a cutaneous disorder characterized by skin fragility, vesiculation, and scarring in sun-exposed areas, particularly the face and hands. Pseudoporphyria mimics the photosensitivity reaction observed in the cutaneous porphyrias. However, patients with this disorder have normal porphyrin metabolism. There are several reports of naproxen-induced pseudoporphyria in patients with JRA (2–8), but the natural history of this disorder has not been previously documented. The purpose of this study was to determine the long-term outcome of facial scarring in a cohort of patients with naproxen-induced pseudoporphyria.

A cohort of 9 patients (7 girls and 2 boys, ages 2–11) with pseudoporphyria was identified in a 6-month prospective study of a population of patients with JRA (December 1991–May 1992) at the Izaak Walton Killam (IWK)–Grace Health Centre (5), and followed up for 5 years. All patients met the American College of Rheumatology criteria for JRA (9,10) and had been treated with naproxen (mean dosage 14.8 mg/kg/day). Naproxen was discontinued for all patients upon diagnosis of pseudoporphyria. True porphyria was excluded in all patients by quantitative porphyrin assay for stool coproporphyrin and protoporphyrin, 24-hour urinary excretion of uroporphyrin, and free erythrocyte protoporphyrin in the blood. Skin phototype was assessed based on the classification by Fitzpatrick, which grades an individual's burning and tanning tendency according to his or her response to an initial sun exposure (grades I–VI) (11). All patients had phototype I or II,

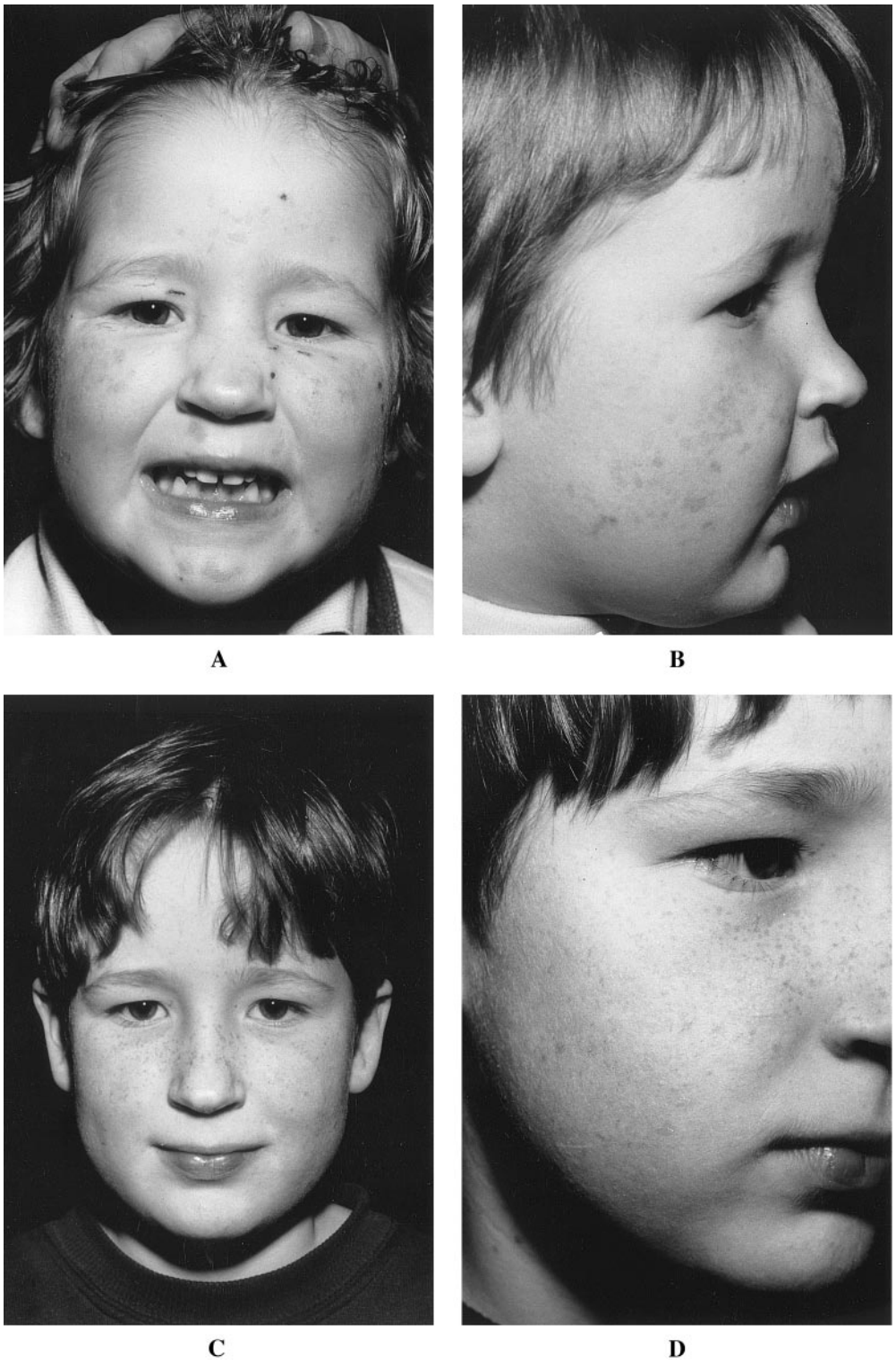

Figure 1. Course of improvement in facial scarring for a young juvenile rheumatoid arthritis (JRA) patient with pseudoporphyria. **A,** At diagnosis of pseudoporphyria, this 3½-year-old girl with JRA had a blistering skin rash and multiple superficial scars on her face. Reproduced, with permission, from ref. 5. **B,** At 4-month followup, multiple scars persisted on her cheeks and forehead. **C** and **D,** At 5-year followup, there is marked improvement. Scars on the cheeks and forehead are barely visible.

i.e., they were fair-skinned individuals who always or usually burn and have no tan or minimal tan. Followup assessments were performed at 1–4 months, 12–14 months, and 54–60 months after the diagnosis of pseudoporphyria. Each assessment consisted of a patient/parent interview, completion of a questionnaire, physical examination for manifestations of pseudoporphyria, and serial photography. Patients were assessed for the status of previous scarring, the presence of ongoing skin fragility, and the occurrence of new vesiculation and/or scarring. The study was approved by the IWK–Grace Health Centre Research Ethics Committee, and informed consent was obtained from the parents and/or patients in all cases.

At diagnosis, all 9 patients had typical angular and linear, depressed, superficial facial scars characteristic of erythropoietic protoporphyria. All lesions occurred in sun-exposed areas. Three of 9 patients had severe scarring (multiple scars, very prominent), 3 had moderate scarring (multiple scars, easily detectable), and 3 had mild-to-moderate scarring (multiple scars, detectable only with careful examination). Scars were first detected by parents only in the cases of severe scarring. In all other patients, they were detected on routine followup visits.

At 1–4-months followup, all patients had persisting facial scars. Only 1 patient continued to develop new scars. At 1-year followup, all patients had improved, and none reported ongoing skin fragility or new scar formation. The degree of residual scarring was severe in 1 patient, moderate in 3 patients, and mild in 5 patients. At 5-year followup, skin lesions showed ongoing resolution. Two of the 3 patients who were initially severely affected still had moderate scarring, while the remaining 7 patients had only very mild persistent scarring. No patients had abnormal skin fragility or new scar formation. Figure 1 illustrates the marked improvement in facial scarring at the 5-year followup. At that time, no child and only 3 parents expressed any concern about permanent facial scarring. None of the parents or patients reported using creams, lotions, or other interventions to treat remaining scars, although 7 reported that they used sunscreen regularly.

Our study demonstrates that the facial scarring of pseudoporphyria improves slowly with time. However, it can persist for up to 5 years after naproxen therapy is discontinued. Patients with more severe scarring at diagnosis are more likely to have more obvious scarring at 5-year followup. After cessation of naproxen therapy, skin fragility, vesiculation, and new scar formation usually resolve, but these features occasionally may persist for several months.

Although several studies of naproxen-induced pseudoporphyria in children with JRA have suggested that blistering and new scar formation ceased after naproxen was discontinued (2,3,8), a recent study found 4 children with pseudoporphyria who continued to develop new blisters for up to 5 weeks after naproxen was discontinued (7). In 2 of these patients, skin fragility persisted for 4–6 months after naproxen treatment was stopped. Similarly, in our study, 1 of the severely affected patients had ongoing scar formation during the first 4 months after naproxen was discontinued. Although our patient was treated with tolmetin during this 4-month period, it is unlikely that this contributed to the ongoing pseudoporphyria, since he developed no new scars during the subsequent 5 years of treatment with tolmetin. In contrast with tolmetin, which has not been reported to cause pseudoporphyria, ibuprofen, a phenylpropionic acid–derivative NSAID, has been reported to cause pseudoporphyria. Although our study showed no problems in the 2 patients whose therapy was changed from naproxen to ibuprofen, patients should be monitored for worsening of pseudoporphyria if this medication is used. Naproxen was not restarted for our patients during the study period because of reports of exacerbation of pseudoporphyria with reintroduction of naproxen (2). Exacerbations have also been observed with exposure to sunlight (7), which was the case in 2 of our patients. We therefore recommend sunscreen (sun protection factor $\geq$30) for our naproxen-treated patients, particularly for fair-skinned patients (phototypes I and II), since they appear to be at higher risk for pseudoporphyria.

We conclude that the scars of pseudoporphyria fade with time with no intervention except discontinuation of naproxen, although faint facial scars may persist for up to 5 years. Because the severity of long-term scarring depends on the extent of scarring at diagnosis, it is essential for physicians, parents, and patients to recognize this complication of naproxen and be aware of the natural history of pseudoporphyria.

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