**Pulmonary Sequelae in Procaine Amide Induced Lupus-like Syndrome**


A 35-year-old man with a lupus-like syndrome secondary to procaine amide therapy sustained apparent permanent pulmonary sequelae despite discontinuation of the drug and corticosteroid therapy. Pulmonary function evaluation showed a restrictive defect with associated impaired diffusion. Previous reports, in contrast, have emphasized the reversibility of this syndrome.

The occurrence of a reversible lupus-like syndrome in association with procaine amide therapy has been reported a number of times since the initial report by Ladd in 1962.1 Features distinguishing the syndrome from idiopathic systemic lupus erythematosus have been the lack of renal involvement and the disappearance of symptoms and serologic abnormalities upon withdrawal of the drug. Recently we have had the opportunity to see a patient who appears to have sustained permanent sequelae in the lungs and pleura in the form of a combined restrictive diffusion defect following a lupus-like syndrome secondary to procaine amide therapy. This occurred despite a course of corticosteroid therapy. The documentation of permanent disability following this type of drug reaction emphasizes the importance of recognizing the problem at an early stage.

**CASE REPORT**

A 35-year-old white aircraft controller had been in good health except for episodes of paroxysmal tachycardia since childhood. In October of 1963 the patient was recognized as having Wolff-Parkinson-White syndrome with intermittent atrial tachycardia. He was given procaine amide at that time in a dosage of 250 mg t.i.d. and he continued on the drug with good control of the paroxysmal tachycardia. In September 1966, the patient initially complained of arthralgias, generalized fibrositis, and proximal muscle weakness and aching.

On May 18, 1967, he presented to the Madison, Wisconsin General Hospital with severe substernal pain of a pleuritic type. On examination of the patient, a loud basilar pericardial friction rub was noted. Electrocardiographic changes compatible with acute pericarditis were present. The chest x-ray film showed evidence of pleural reaction in each base (Fig 1). Previous annual chest films had been reported as normal through 1966. Multiple lupus erythematosus cell preparations were positive and the antinuclear factor was also strongly reactive. The urinalysis and blood urea were, however, normal. The LDH, bilirubin, serum glutamic oxaloacetic transaminase (SCOT), serum glutamic pyruvic transaminase (SGPT) and sulfobromsulfalein (BSP) dye tests were all within normal limits.

The patient's procaine amide therapy was stopped at the time of admission to the Wisconsin hospital and he was started on large dosages of corticosteroids. His symptoms were rapidly relieved on this regimen. He was transferred to our hospital on June 8, 1967.

Detailed pulmonary function evaluation shortly after admission here showed evidence of a combined restrictive diffusion defect. The vital capacity was reduced to 52 percent of the predicted normal, while the maximal breathing capacity was normal. The steady state carbon monoxide diffusion capacity was decreased to 12.5 from a predicted 26 (normal range 19.5 to 32.5). The electrocardiographic changes had reverted to normal and by late June 1967 the chest x-ray film only showed evidence of pleural reaction. The corticosteroids were discontinued after a total of 40 days of therapy as the patient was asymptomatic except for some dyspnea on strenuous exertion.

Within ten weeks from the time of discontinuation of the procaine amide, the LE cell test and antinuclear factor determinations were negative and have remained so. However, despite any clinical or laboratory evidence of active disease the patient continued to show minimal dyspnea on strenuous exertion when he was last seen in March of 1968. In addition, the vital capacity has remained reduced to approximately 50 percent of predicted normal. The carbon monoxide diffusion capacity has shown some improvement but remains abnormal ten months after the drug was discontinued, being 17.8. The arterial PO2 likewise remains abnormal, being 78 mm Hg at rest on the most recent determination. The most recent chest film still shows minimal residual pleural reaction on the left side (Fig 2).

Of considerable additional interest is the fact that the patient's brother, at age 16, developed severe pericarditis, arthritis, and pleuritis, following a course of penicillin therapy. It is unknown whether or not this was the procaine amide form of that drug. Several aspirations of the pleural fluid were required before the illness resolved. Repeated LE cell preparations were negative. On follow-up examination two years later, this boy was asymptomatic. The electrocardiogram and chest roentgenogram were within normal limits.

**COMMENTS**

The patient's lupus-like syndrome which developed secondary to the procaine amide therapy is very similar to other cases reported in the recent literature (Table 1). Arthralgias, which were a prominent symptom early in the course of his disease, have been noted in all previously reported cases. This has generally tended to be an early symptom and therefore can be regarded as a warning in the patient on procaine amide therapy that an adverse reaction is developing. If the syndrome is recognized at this stage, involvement of vital organs which may occur with further therapy may then be avoided.

In addition to arthralgias and arthritis, other manifestations of polyserositis may be seen. The peri-
carditis experienced by our patient is certainly not unexpected in any patient developing a lupus-like syndrome, although it was noted only once in the 16 cases previously reported.

The pleuritis and parenchymal pulmonary involvement, as occurred in our patient, have also been frequently seen in previously studied patients. However, the evidence of diffusion block and associated reduced arterial partial pressure of oxygen have not been previously noted.

The absence of renal involvement as seen in our patient has been found to be characteristic of those with the lupus-like syndrome secondary to procaine amide; this is in contrast to idiopathic lupus erythematosus where renal involvement is common.

The long latent period of 35 months before the onset of the lupus-like symptoms in our patient was also of interest. Previously reported cases have shown latent periods varying from 2 to 22 months. This emphasizes that the clinician should be constantly alert for this untoward drug reaction since there is apparently no relation in its development to the duration of drug therapy.

It has been emphasized in previous descriptions of this syndrome secondary to procaine amide that significant chronic residuals of the disease have not remained once the drug has been discontinued, and in some cases a course of corticosteroids administered. Our patient promptly improved in all respects upon discontinuation of the drug and institution of corticosteroid therapy. Without further evidence of activity of the disease, corticosteroid therapy was discontinued after six weeks. His LE cell preparations and antinuclear factor tests which had been strongly positive were all negative within ten weeks after discontinuing the procaine amide.

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**Table 1—Summary of Clinical Data on Patients with Procaine Amide Induced Lupus-like Syndrome**

<table>
<thead>
<tr>
<th>Author</th>
<th>Daily Dosage of Procaine Amide</th>
<th>Mos. of Adm. of Drugs Before Symptoms</th>
<th>Duration of Symptoms in Months Before Symptoms</th>
<th>Major Symptoms &amp; Signs</th>
<th>Extent and Time of Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ladd1</td>
<td>3 gm</td>
<td>3</td>
<td>4</td>
<td>Rash, arthralgias; pleuritis with effusion, pleuritis with effusion, arthralgias</td>
<td>Complete in 10 wks</td>
</tr>
<tr>
<td>Hahn²</td>
<td>2.0-5.0 gm</td>
<td>10</td>
<td>Not dsc. Started on corticosteroids after 2 mos of symptoms One wk</td>
<td>Urticaria, fibrositis, arthritis</td>
<td>Complete while on corticosteroids</td>
</tr>
<tr>
<td>Kaplan et al² Case 1</td>
<td>1.5-2.0 gm</td>
<td>9</td>
<td>3 mo course of therapy with first; 7 wks with second</td>
<td>Migratory arthralgias, erythematous rash, myalgia, pleuritis, splenomegaly</td>
<td>Symptomatically complete in 1 mo</td>
</tr>
<tr>
<td>Kaplan, Case 2</td>
<td>3.0 gm</td>
<td>3</td>
<td>3</td>
<td>Arthralgias</td>
<td>Asymptomatic decreasing splenomegaly</td>
</tr>
<tr>
<td>Kaplan, Case 3</td>
<td>0.75-20.0 gm</td>
<td>5</td>
<td>6</td>
<td>Arthralgias, pleuritis with effusion; pulmonary infiltrate, pericarditis</td>
<td>Asymptomatic within a few days of corticosteroid therapy (which was continued for 2 yrs)</td>
</tr>
<tr>
<td>Kaplan, Case 4</td>
<td>0.75-2.0 gm</td>
<td>1</td>
<td>11</td>
<td>Arthralgias, myalgia, purpura</td>
<td>Complete in 3 mos (still on prednisone)</td>
</tr>
<tr>
<td>Paine³ Case 1</td>
<td>1.5</td>
<td>3</td>
<td>0</td>
<td>Arthralgias, pleuritis</td>
<td>Complete within 2 mos</td>
</tr>
<tr>
<td>Paine, Case 2</td>
<td>2.0</td>
<td>3/4 wks</td>
<td>0</td>
<td>Fever, arthralgias</td>
<td>Complete within wks</td>
</tr>
<tr>
<td>Paine, Case 3</td>
<td>1.5-1.0 gm</td>
<td>8</td>
<td>3</td>
<td>Arthritis, pericardial pain</td>
<td>Complete (marked improvement in one wk)</td>
</tr>
<tr>
<td>Paine, Case 4</td>
<td>0.5 gm</td>
<td>22</td>
<td>15</td>
<td>Arthralgias, pleuritis with effusion</td>
<td>Complete except for minimal pleural reaction</td>
</tr>
<tr>
<td>London &amp; Pincus, Case 1</td>
<td>1.5 gm</td>
<td>15</td>
<td>13</td>
<td>Arthralgias</td>
<td>Complete in 4 wks</td>
</tr>
<tr>
<td>London &amp; Pincus, Case 2</td>
<td>Not stated</td>
<td>1</td>
<td>0</td>
<td>Arthralgias</td>
<td>Complete after several wks</td>
</tr>
<tr>
<td>Prockop⁷</td>
<td>2.0-5.0 gm</td>
<td>22</td>
<td>13</td>
<td>Arthralgias, myalgia, migratory arthralgias, fever, hepatosplenomegaly</td>
<td>Complete in 2 wks</td>
</tr>
<tr>
<td>Hanlon⁸</td>
<td>0.75-4.0 gm</td>
<td>12</td>
<td>Not stated</td>
<td>Arthralgias, fibrositis, pericarditis, myalgia</td>
<td>Complete in 2 mos</td>
</tr>
<tr>
<td>Byrd &amp; Schanzer</td>
<td>1.0 gm</td>
<td>35</td>
<td>9</td>
<td>Arthralgias, fibrositis, pericarditis, myalgia</td>
<td>Incomplete in 10 mos</td>
</tr>
</tbody>
</table>

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amide. However, the vital capacity, carbon monoxide diffusion capacity, and arterial oxygen studies have remained abnormal over a nine month period of follow-up. Serial chest roentgenograms have shown apparent consolidation of the pleural reactions into scar tissue. The patient remains symptomatic on rapid walking and at present it appears unlikely that further improvement can be expected. The only similar case previously reported with residual pleural involvement was Paine's fourth case. This elderly woman still has evidence of a minimal pleural reaction in the right base on chest roentgenogram three years after being off the drug. Pulmonary function studies are not available on this patient, but she has no respiratory symptoms (personal communication from Doctor Paine.)

It seems unlikely that this patient represents a case of classic lupus erythematosus that was precipitated by the drug. In all other aspects other than the failure to completely resolve his diffusion defect, and even more strikingly his restrictive defect, our patient is similar to those previously reported with the reversible syndrome. It would appear his residual abnormalities are related to tissue fibrosis and scarring rather than to active inflammation.

There has been considerable discussion as to whether drug-induced lupus syndromes tend to occur in those with genetic predispositions to such reactions. This is certainly suggested in our patient by the similar clinical reaction his brother sustained after a course of penicillin therapy.

ACKNOWLEDGMENTS: We wish to acknowledge the contributions to this case from Drs. G. Thomas Pfehler and L. T. Giles at the Madison General Hospital and also to Dr. Charles Prasser of Baton Rouge, La., who supplied the information in regard to our patient's sibling.

REFERENCES


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