

## THE MONONUCLEOSIS SYNDROME IN LEPROSY PATIENTS TREATED WITH SULFONES

D. L. LEIKER, M. D.  
*Chief, Division of Leprosy Control,  
Netherlands New Guinea*

In 1949 Lowe (2), in Nigeria, described a complication of the sulfone treatment of leprosy patients which was clinically similar to mononucleosis infectiosa, a disease frequently seen in that country among children and young people but seldom among adults. This complication had occurred in 12 per cent of his patients at that time. Dermatitis of the exfoliative type was seen in 2 per cent. These attacks were seen almost exclusively between two and five weeks after the beginning of the sulfone treatment. Later on, he also saw the same type of dermatitis without typical features of infectious mononucleosis. All of his patients recovered after the sulfone treatment was withdrawn.

Lowe considered this condition to be true attacks of mononucleosis infectiosa precipitated by sulfone drugs. It is surprising that this complication has not been mentioned since then by other leprologists.

In 1955, at the leprosarium at Mie, I saw two patients corresponding to those described by Lowe. One of them died, so the complication is not always a harmless one.

CASE 1. Patient E. K., female, 25 years old, with major tuberculoid leprosy, bacteriologically positive (1+), complained of headache five weeks after the first dose of DDS was given. Her temperature was normal. Blood smears were negative for malaria. The next day the temperature rose to 39°C. During the following two weeks she had irregular pyrexia between 38° and 40°, slowly decreasing in the next two weeks. It was five weeks before the temperature was normal again.

On the fifth day of her illness a red, papular rash appeared, seen first on the back but within two days covering the whole body. Two days later the body was covered with very small whitish scales. Besides slight itching and a dry cough, however, her main complaint was only severe headache.

On physical examination there were no abnormal findings in the lungs. There was moderate general enlargement of the lymph nodes, most marked in the neck, and enlargement of the spleen (Schüffner II). During the first three days after the dermatitis appeared the white blood cell count was between 8,000 and 10,000, with 60 per cent mononuclear cells. In the following week there was an increase to 29,000 leucocytes, of which 70 per cent were mononuclears. At that time the lymph node and spleen enlargement became more marked, and on percussion the mediastinum was found to be broadened. The patient felt more ill, and there was moderate dyspnea besides the persistent cough, without other abnormal findings in the lungs.

In the following two weeks the temperature slowly decreased, all symptoms subsided, and blood count became normal. One month later there was a short relapse, although she had not taken DDS again. For four days she had fever, and the scaling dermatitis recurred in moderate degree. After recovery the patient was treated with thiosemicarbazone without further complications.

CASE 2. Patient L. P., male, 25 years old, with atypical lepromatous leprosy, complained of fever four weeks after taking the first dose of DDS. His temperature

was normal when he was admitted to the ward, but later the same day it increased to 39.5°C. On the fourth day after admission it rose to 40.6°. The leucocyte count then was 7,000, mononuclear cells 42 per cent. The patient had no complaints besides fever, but on the following day an itching papular dermatitis occurred, soon covering the whole body; but apart from some itching there still were no complaints. The temperature decreased to 38.5°.

On the eighth day of his illness there was moderate general enlargement of the lymph nodes and spleen, and damage of the liver was evidenced by slight jaundice. The leucocyte count was only 6,000, but 87 per cent of the cells were mononuclears.

On the night of the eighth day the patient suddenly felt extremely ill. The lymph nodes were acutely enlarged, especially those in the neck and the bottom of the mouth. He could hardly speak any more, and there was marked dyspnea. The body was covered with bullae, and the jaundice was severe. The next day the temperature rose again to 40.5°. The leucocyte count was 3,000, with 90 per cent mononuclears.

The patient was treated with cortisone, whereupon the bullae disappeared and desquamation of the skin condition occurred. The temperature remained high, however, and the percentage of mononuclear cells rose to 96. He died unconscious two days afterwards.

Although most of the physicians in New Guinea are not unfamiliar with mononucleosis infectiosa, there is no record that this disease has been observed in this country. Local circumstances did not permit our doing the Paul-Bunnell and Barrett adsorption tests, which however are not specific. The evidence of Lowe was based mainly on the Paul-Bunnell test.

It is surprising that now, when sulfones are being used on a large scale, this complication has not been mentioned again from other countries, especially those in which mononucleosis infectiosa is prevalent. Regarding Lowe's experience in Nigeria, where that infection seems to be fairly common, it is hard to understand why it was not seen among patients who had been treated with sulfones for periods longer than two months. In my own cases the onset was five and four weeks, respectively, after the beginning of treatment. One would not expect all of these patients to have had a latent infection when they started the treatment.

Similar complications have been described in tuberculosis patients treated with PAS (1, 3-7)—also exclusively within two months after the beginning of treatment. It seems necessary to consider the possibility that the condition in these cases was not true mononucleosis infectiosa, but a delayed allergic reaction that can be induced by such drugs as the sulfones and PAS. Therefore, until this matter is cleared up, I prefer to use the term "mononucleosis syndrome" for this phenomenon.

Mononucleosis patients usually recover. However, one of the two patients here reported died after a severe acute attack, although the onset did not indicate such a serious development.

In the first week it is difficult to diagnose this complication. It seems wise to pay close attention to blood counts in the first months of treatment with sulfones, especially when patients complain of headache, fever and dermatitis without reactional conditions of the skin lesions.

Since cortisone had some influence on the dermatitis in my second case, and since the symptoms can be explained by reticuloendothelial hyperactivity of allergic origin, antihistaminics, cortisone, or ACTH, given as early as possible, should be the treatment of choice.

#### SUMMARY

Two young adult leprosy patients showed severe symptoms similar to mononucleosis infectiosa within five weeks after treatment with DDS was started. One of the patients had a short relapse one month later, although sulfone treatment was not resumed, but then she recovered completely. The second patient died after 10 days. He had developed a bullous dermatitis, but although that subsided under cortisone treatment he died of severe liver damage and agranulocytosis.

Lowe described this condition in Nigeria in 1949, and considered it to be true mononucleosis infectiosa precipitated by the sulfone treatment. It has not been mentioned by other leprosy workers since then.

This phenomenon seems to be limited to the first two months of treatment, whereas if it were true mononucleosis infectiosa one would expect at least some new cases among patients in later periods of treatment in countries where mononucleosis is endemic. Furthermore, similar symptoms have been described after the administration of PAS, also within two months after the first dose.

For these reasons, and because not a single case of mononucleosis infectiosa has been reported from Netherlands New Guinea in the past, it seems necessary to consider the possibility that this phenomenon does not represent true infectious mononucleosis, but that it is a delayed allergic reaction of the reticuloendothelial system induced by sulfones and other drugs. For the present, therefore, I prefer to use the term "mononucleosis syndrome" instead of mononucleosis infectiosa, the latter being reserved for cases in which there is no doubt about the infectious nature of the condition.

Since in one patient the dermatitis subsided after cortisone and since an allergic condition is suspected, it would seem that early treatment with antihistaminics, cortisone, or ACTH is indicated.

**ADDENDUM:** Since the foregoing report was prepared, a third, mild, case of mononucleosis syndrome has been seen among the leprosy patients here, this one at Manokwari.

**CASE 3.** Patient A. M., female, 26 years of age, with minor tuberculoid leprosy, was put under DDS treatment on October 9, 1956, the dose 100 mgm. twice a week, increased 100 mgm. weekly. After about seven weeks, on November 16th, she complained of fever and itching, and a few days later the leucocyte count was found to be 9,800, with 66 per cent mononuclear cells. There was a generalized dermatitis desquamativa with exfoliation over the right elbow, and edema of the face. The spleen was moderately enlarged, the lymph nodes of the neck, axillae and groins more markedly so. The temperature ranged irregularly between 37° and 38.5°.

Treatment with cortisone was started at once. The itching was completely relieved

within 48 hours, and the skin showed a dry, grayish, scaly condition. The edema and fever took a few more days to subside. Two weeks later there was still a leucocytosis of 21,500, but the number of mononuclear cells tended to be normal. Five weeks after onset the count was 8,600, with 30 per cent mononuclears.

#### RESUMEN

Dos jóvenes adultos leprosos revelaron síntomas graves semejantes a mononucleosis infecciosa en término de cinco semanas de la iniciación del tratamiento con DDS. Uno de los enfermos tuvo una breve recidiva un mes después, aunque no se había reanudado la sulfonoterapia, pero la enferma se curó por completo. El segundo enfermo falleció al cabo de 10 días, habiendo manifestado una dermatitis vesicular, y aunque ésta cedió a la cortisonoterapia, el sujeto murió de intensa lesión hepática y agranulocitosis.

Lowe describió esta dolencia en Nigeria en 1949, considerándola verdadera mononucleosis infecciosa precipitada por la sulfonoterapia, sin que la hayan mencionado otros leprólogos desde entonces.

Este fenómeno parece limitarse a los dos primeros meses de tratamiento, en tanto que si fuera verdadera mononucleosis infecciosa, serían de esperar a lo menos algunos casos entre los enfermos en períodos más tardíos de tratamiento en países en que la mononucleosis es endémica. Además, se han descrito síntomas semejantes a continuación de la administración de PAS, también en término de dos meses de la primera dosis.

Por estas razones, y por no haberse comunicado un solo caso de mononucleosis infecciosa de la Nueva Guinea holandesa en el pasado, parece necesario considerar la posibilidad de que este fenómeno no represente verdadera mononucleosis infecciosa, sino más bien una reacción alérgica tardía del sistema retículoendotelial inducida por sulfonas y otras drogas. Por consiguiente, préfiérese de momento utilizar el término de "síndrome mononucleótico" en vez de mononucleosis infecciosa, reservando el último para casos en los que no cabe duda acerca de la naturaleza infecciosa de la dolencia.

Como en un enfermo la dermatitis cedió ante la cortisona y como se sospecha un estado alérgico, parece que está indicado el tratamiento temprano con antihistamínicos, cortisona o HCTS.

(Desde que se escribiera este trabajo, se ha observado el tercer caso de la dolencia, según se relata en un addendum.)

#### REFERENCES

1. LICHTENSTEIN, M. R. and CANNEMEYER, W. Severe para-aminosalicylic acid hypersensitivity simulating mononucleosis or hepatitis. *J. American Med. Assoc.* **152** (1953) 606-607.
2. LOWE, J. and SMITH, M. The chemotherapy of leprosy in Nigeria. With an appendix on glandular fever and exfoliative dermatitis precipitated by sulfones. *Internat. J. Leprosy* **17** (1949) 181-195.
3. SJOUKES, P. Een ziektebeeld gelijkend op mononucleosis infectiosa, veroorzaakt door P. A. S. *Nederlandsch tijdschr. geneesk.* **96** (1952) 2001-2006.
4. SJOUKES, P. Clinisch en haematologisch beeld gelijkend op mononucleosis infectiosa tijdens toediening van P. A. S. *Nederlandsch tijdschr. geneesk.* **96** (1952) 2389-2390.
5. STEEL, S. J. Acquired sensitivity to para-aminosalicylic acid. *British Med. J.* **1** (1952) 415-416.
6. VAN DONK, H. J. Klierkoorts van Pfeiffer en overgevoeligheid tegenover P. A. S. *Nederlandsch tijdschr. geneesk.* **96** (1952) 2199-2203.
7. WARRING, F. C., JR. and HOWLETT, K. S., JR. Allergic reactions to para-aminosalicylic acid; report of seven cases, including one case of Löffler's syndrome. *American Rev. Tuberc.* **65** (1952) 235-249.