SUDDEN APPEARANCE OF A LEPROMATOUS ERUPTION DURING PROLONGED ADMINISTRATION OF STILBESTROL IN A CASE OF UNSUSPECTED LEPROSY

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The principal object in reporting the following case, which presents a number of unusual features, is to put on record the possibility of an etiological relationship between the administration of the synthetic estrogen stilbestrol (4,4′-dihydro-α: β-diethylstilbene) over a period of many months and the sudden dermal manifestation of previously unsuspected leprosy in an elderly man, who was thought to be suffering from carcinoma of the prostate gland.

CASE REPORT

Patient S. (Registration No. 60721/46), an intelligent and well-educated man, was born in the West Indies in 1863. His father was French and his mother a Negress. He spent most of his life in various parts of the French colonial empire, particularly French West Africa, and in the West Indies. He settled in metropolitan France between the two world wars, and in 1940—then aged 77 years—came as a war refugee to England, where he lived in a home for old people. He appeared at that time to be in excellent health, and his general condition was unusually good for a man of his age. He stated that he had never had any ill health.

At the beginning of August 1946 he came to the Radcliffe Infirmary, Oxford, complaining of slight difficulty in urinating. He gave a history of having had to rise to pass urine two or three times nightly for some years, and said that during this period he had from time to time, in the summer months, suffered from increased frequency of micturition by day as well as by night, associated with a scalding sensation and turbidity of the urine. His main complaint, however, was of a recent decrease in the strength of the stream, interruption of the flow and some after-dribbling.

Rectal examination revealed moderate, uniform enlargement of the prostate gland, which was hard and nodular. No other abnormalities were found clinically. A radiograph showed a few small translucent areas in the neck of the right femur, but the appearance did not suggest metastases, and there was no abnormality of the left femur or of the innominate bones, sacrum or lumbar vertebrae. Urethrography gave no information, as a spasm prevented the radio-opaque medium from passing farther back than the junction of the anterior and membranous parts of the urethra. No

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abnormal constituents were found in the urine. The opinion was formed that the prostate was probably carcinomatous, but chronic prostatitis was considered as a possible alternate diagnosis. In view of his age and of the minor nature of his symptoms it was not thought it necessary to perform a biopsy or to recommend any other surgical intervention until the effect of medical treatment had been observed.

Treatment with stilbestrol, 2 mgm. three times a day by mouth, was started on August 3, 1946. Four weeks later, although there was no subjective improvement, the prostate was thought to be rather smaller and softer. The patient was not seen again at the hospital until April 1947; by this time his symptoms had completely disappeared, and the prostate felt soft and was of normal size. The dosage of stilbestrol, administration of which had been continued without interruption by his medical attendant, was now reduced to 2 mgm. twice a day, and it was continued at this level until September 1947.

The patient next attended the hospital on September 8, 1947, when he was referred to the Dermatological Department because of the rapid development of a skin eruption during the preceding two or three days. He had never previously had any skin disease. There had been no return of the urinary symptoms, and his general health appeared to be good. Examination showed numerous but widely scattered, firm, non-tender, reddish nodules in the skin of the arms and legs and of the dorsum of each hand and foot. The nodules were freely movable over the underlying structures. They were slightly elevated above the level of the surface of the surrounding skin. All the lesions were of the same order of size, approximately 0.5 cm. in diameter, but their limits were not well defined. The only other abnormality of the body surface was a diffuse, reddish flush of the front of the chest, said by the patient to have appeared at the same time as the nodules on the limbs. There was no demonstrable disturbance of skin sensation.

In view of the patient's history it was considered that the skin nodules either were metastatic deposits of carcinoma or represented a drug-sensitization dermatosis complicating the stilbestrol therapy. Under local anesthesia a nodule was excised from one forearm for diagnostic purpose. When the sections were examined and leprosy diagnosed the patient was sent for, but he had left the country and it has not been possible to trace his whereabouts.

PATHOLOGICAL FINDINGS

Gross appearance.—The specimen (laboratory No. RISH 3181/47), a diamond-shaped piece of skin measuring 2.5 x 1.0 cm., had at its center a firm nodule, 0.5 cm. in diameter. From its periphery the nodule sloped up gently from the level of the surrounding skin-surface to a maximal height of 0.2 cm. The skin at the center of the nodule was depressed to a depth of about 0.1 cm. over an area 0.25 cm. across. When bisected the nodule presented a yellowish-white, homogeneous cut surface, without sharp delimitation from the dermis.

The bisected specimen was fixed in formol-saline solution (4 per cent formaldehyde), and paraffin sections were prepared.

Histological findings.—The nodule proved to be a rather poorly circumscribed granuloma, separated by a narrow zone of uninvolved connective tissue from the slightly atrophic overlying epidermis. The lesion was made up of several large, coalescent, densely cellular aggregates which had formed in the interstitium of the dermis, separating, compressing and to some extent destroying its fibrous components and distorting the epidermal appendages. The great majority of the cells were large histiocytes; most of the others were lymphocytes, which were most numerous at the periphery of the granulomatous area, where there were also a few plasma cells. No unusual prominence of blood vessels was present to account for the reddish hue of the nodules observed clinically.

The histiocytes were closely packed and the cellular infiltrate was of fairly uniform appearance, although in places at the periphery of the aggregates the cells showed more or less epithelioid metamorphosis. Occasional small folliculoid congeries, resembling very early tuberculous follicles, were present in the dermis in the vicinity of the main nodule. No multinucleated cells were seen, and there was no necrosis or fibrosis. Many of the histiocytes were of unusual morphology, containing vacuoles which gave a foamy appearance to the cytoplasm. In some cells a single large vacuole displaced the nucleus to the periphery. The larger vacuoles usually contained finely granular inclusions, which were faintly eosinophilic or, more often, hematoxyphilic. In Ziehl-Neelsen preparations these inclusions were seen to consist of masses of closely packed bacilli, the arrangement, morphology and staining reaction of which were those of *Mycobacterium leprae.* The bacilli were also well shown by Giemsa's stain.[2] They were present in varying numbers in the cytoplasm of the histiocytes and also lying free in the interstitium. Globi were numerous. Apart from the granulomatous foci, bacilli were scattered in great numbers throughout the tissues. Isolated Virchow cells packed with the organisms were seen, particularly adjacent to blood vessels, even at the margin of the specimen a centimeter or so distant from the nodule itself. Here and there bacilli were present within and between the cells of all layers of the epidermis and in the stratum corneum. They were abundant in the epithelial cells of the sweat glands and hair follicles.

The histological findings were those characteristic of a young, cellular lepromatous lesion. No coexistent pathological process of different nature was apparent.

DISCUSSION

This case is of interest from both the clinical and the theoretical points of view. From the clinical aspect it must be admitted that the unforeseeable circumstances of the patient's departure from the country before the biopsy specimen could be studied made it impossible to obtain a more detailed history, or to investigate his condition fully. There is, therefore, no exhaus-

[2] I have found Giemsa's stain to be of considerable value in the demonstration of the leprosy bacillus, although the use of the stain for this purpose appears not to be widely known. In a personal communication concerning this point, Dr. H. W. Wade has mentioned to me his similar experience in the use of this technique.

tive information about his medical history and his environment prior to 1940, and so no critical study could be made of any facets possibly relevant to the leprous infection. He had, however, stated that he had never had any illness of any sort before coming to England in 1940, and he had no illness after his arrival here other than the urinary disturbance described in the case report, until the appearance of the exanthem which revealed the presence—unsuspected until then—of leprosy.

Clinical examination at the time when he had developed the skin eruption revealed no lesions of the body surface except the nodules on the limbs and the erythema of the chest. While there is no record of any other noteworthy features in respect of his appearance, it is possible that an examination made with a diagnosis of leprosy under consideration might have shown other stigmata of this disease. As it was, a nodular eruption of this type, suddenly appearing in an elderly man who otherwise appeared to be in excellent health but who was known to be under stilbestrol treatment for presumed carcinoma of the prostate, appeared reasonably to be attributable either to neoplastic metastases or to sensitization of the tissues to the drug. In noting that leprosy was not considered in the differential diagnosis it must be remembered that this patient, whose appearance gave no hint of his life abroad, was observed in a country where this infection is seen only with extreme rarity.

It is of interest to note that, even when the prostate was first examined *per rectum*, the diagnosis of prostatic cancer was made with the qualification that the findings on palpation were not so characteristic of carcinoma as to exclude the alternative diagnosis, that of a purely inflammatory condition. As there were no grounds for surgical intervention, and as, in view of the patient's age, biopsy was not considered to be essential, no opportunity presented to put the clinical impression to the test of histological examination. Furthermore, the small areas of radio-translucency in the neck of one femur were not radiologically suggestive of a neoplastic process. In the light of the microscopic demonstration of the leprous nature of the skin lesions, it may be that there was no carcinoma, and that the patient had indeed a lepromatous prostatis and ostieitis; but there is no justification for going farther than merely to mention this as a possibility, which would not explain the complete disappearance of the urinary symptoms and the return of the prostate to normal size and consistency as shown by rectal examination.

During the years which he spent in England the patient was not in contact with any known persons with leprosy, nor were any of the other residents of the home where he lived known to have had any such contact or to have been in any country where leprosy is endemic. He himself, however, had spent a considerable part of his long life in such countries. From the available records of his case it can only be assumed that his infection had been present, but latent, for some time. Its sudden clinical onset was not associated with any symptoms other than the appearance of the skin eruptions; he had neither fever nor malaise.

Before the development of the skin lesions, this patient had been taking stilbestrol daily for 13 months, the dosage being 6 mgm. a day from August 1946 until it was reduced to 4 mgm. a day in April 1947, at which level it was continued until September of that year, when the eruptions appeared. Whether there was any association between the prolonged and heavy dosage with this powerful, synthetic estrogen and the sudden clinical manifestation of a hitherto unsuspected infection by *M. leprae* is hypothetical. The observation of this sequence of events may, however, be of interest to leprologists in relation to the use of hormone preparations in patients with leprosy, for whom such therapy is indicated as treatment for some intercurrent condition unrelated to the infection with Hansen's bacillus. It also raises the question whether a study of the effects of various hormones, administered to patients with leprosy, might indicate their possible usefulness as an adjuvant to other therapy of the disease.

It is possible that the predominantly male sex incidence of leprosy during the reproductive years of life may be in part determined by hormones. It is also noteworthy that leprosy may make its first clinical appearance during pregnancy or, more often, the puerperium; the infection might quite by chance first become overt at such a time, but it is unlikely that chance is always the explanation. The well-recognized puerperal exacerbations of leprosy which are observed in some patients suggest that conditions may prevail at this time which favor an acceleration in the tempo of progress of the infection, and these conditions may be related to the change in endocrine balance then obtaining.

A case reported by Guillot and Curci (1) is of particular interest in this respect. These authors, among other observations concerning the relationship between leprosy and those physiological states which are peculiar to women, described the

case of a 26-year-old Argentinian patient in whom leprosy appeared for the first time on the second day after the birth of her first child. A tuberculoid macule developed on the left forearm and was followed, a few days later, by a generalized eruption in the form of a tuberculoid leprotic reaction; *M. leprae* was found in the lesions, and the Mitsuda reaction was positive.

Search of the literature has revealed only one previous record of a case in which the first clinical manifestations of leprosy appeared during the course of hormone administration. The case, reported by Iswariah (2), was that of a Muslim woman, aged about 36, to whom 1 grain (65 mgm.) of thyroideum was administered three times a day in the treatment of obesity. After about two months of this treatment, during which her weight fell from 156 lb. (71 kgm.) to about 130 lb. (59 kgm.), she developed paresthesia of the forearm, followed by aching pains in the same site; a papular rash rapidly developed, became nodular, and soon spread from the forearms into the upper arms. Her face became dusky and glistening, and, after a week's fever, thickened patches were found to have appeared in the skin of the dorsum of each foot. *M. leprae* was found in excised nodules and in a nasal smear. It may well have been by chance that this patient's infection became clinically manifest while she was receiving thyroid extract; alternatively, the thyroid medication may have predisposed to development of florid leprosy, either because the disturbance of metabolism resulting from its administration lessened her resistance to established but latent infection, or because of some secondary hormone imbalance caused by the action of the extract on other endocrine glands.

Comparatively little seems to be known of the endocrinological aspects of leprosy. Further studies of the effects upon the development and course of leprosy of physiological and pathological alterations in the endocrine system, and of administration of hormone preparations, may add significantly to our knowledge of this infection.

SUMMARY

The case is reported of a man, aged 84, who in the course of a few days developed a widespread lepromatous eruption on the limbs and an erythema of the chest. There were no other signs of leprosy, and he had no constitutional symptoms. Thirteen months before the skin eruption appeared, prostatic carcinoma had been diagnosed clinically; peroral treatment with stilbestrol

(4,4′-dihydroxy-α: β-diethylstilbene) was started at that time, and continued until the skin lesions appeared. For the first seven and a half months of treatment the dosage of stilbestrol was 2 mgm. three times a day; after this period the dose was reduced to 2 mgm. twice daily.

The possibility is discussed of an etiological relationship between the stilbestrol therapy and the manifestation of the previously latent leprosy.

RESÚMEN

Se reporta un caso de un hombre de 34 años, quien en el transcurso de varios días desarrolló una extensa erupción lepromatosa en las extremidades, y una erupción eritematosa del pecho. No había otros signos de lepra, y el paciente no presentaba síntomas constitucionales. Trece meses antes de presentarse la erupción, se había hecho un diagnóstico clínico de carcinoma prostático; tratamiento con estilbestrol por vía oral fué entances instituído y continuado hasta que aparecieron las lesiones cutáneas. Durante los primeros 7½ meses de tratamiento la dosis de estilbestrol fué de 2 milígramos tres veces al día, luego la dósis fué rabajada a 2 milígramos dos veces al día.

Se discute la posibilidad de alguna relación etiológica entre el tratamiento con estilbestrol y la manifestacion de lepra latente.

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REFERENCES

1. Guillot, C. F. and Curci, A. O. Embarazo y lepra. Consideraciones acerca de la lepra en los estados fisiológicos femeninos. Rev. argentina Dermatosif. **30** (1946) 313-321.
2. Iswariah, V. Acute lepra reaction in course of thyroid medication for obesity. J. Indian Med. Assoc. **14** (1944-45) 58.