MYCOSIS FUNGOIDES TREATED BY MALARIA, TERMINATING IN HODGKIN'S DISEASE

BY

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On May 29, 1931, a dairyman aged 45 presented himself at the skin department of the Middlesex Hospital with a seven-months-old eruption which had begun on the face and eyebrows and later extended to the pubic area, hands, wrists, and legs. The eruption was dry and scaly, except for some areas where moisture and weeping had occurred, thus conforming in its distribution and type to a seborrhoeic dermatitis, the diagnosis recorded at the first visit. As his progress covers a series of admissions to and discharges from the skin and medical wards the sequence of events can best be recorded under four different headings.

First Admission : May 30, 1931, to February 25, 1932

The initial phase of this remarkable history was represented by an eczematous eruption, in places dry, in other regions moist and weeping. The rash was considerable in extent, involving the face, arms, hands, trunk, and legs, and because of the dry scaly appearance in some places and the pronounced flexural distribution was labelled "seborrhoeic eczema." There were during this period fluctuations in the degree and extent of the eruption, with at times marked improvement, followed by an unexpected and disappointing relapse. The degree of itching was considerable and disproportionate, which might have hinted at things to come; and in places, for example over the arm flexures, the margins of the eruption presented an unusual raised or scalloped appearance, contrasting with the more characteristic eczema elsewhere. Although they have no special significance, it may be recorded that in September, 1931, abscesses developed in the calves of both legs, requiring surgical treatment. The Wassermann reaction was negative, and a blood count made on October 6 showed slight anaemia—9,800 leucocytes per c.mm., with the following differential count: polymorphs 61.5%, lymphocytes 23.5%, large mononuclears 0.5%, eosinophil cells 13.5%, and mast cells 1%. As in February, 1932, only some insignificant traces of the eczematous eruption remained, the patient was discharged from the ward to attend the out-patient department. In June, 1932, it was noted that on the trunk there were patches suggestive of the pre-mycotic phase of mycosis fungoides, but this diagnosis was not confirmed and definitely established until March, 1933.

Second Admission : February 23, 1934, to December 5, 1934

Mycosis fungoides was now present in an extensive form, including large sheets of pre-mycotic infiltration of the skin, with tumour formation in many areas. X-ray treatment had been in use from March, 1933, and had hitherto controlled the disease. But now, and for the first time, the eruptive process became so active and involved areas so considerable that x-ray treatment could no longer be employed with safety because the amount required to control the disease must have proved injurious or even fatal to the patient. A point had been reached when seemingly nothing further could be done. In 1933 I had published the beneficial effect of an attack of erysipelas on two cases of mycosis fungoides (MacCormac, 1933). Here seemed a therapeutic hint: the problem, then, was to produce a genuine infection which was accompanied by high fever, of a kind which could be brought under control at will. Malaria therapy seemed to satisfy all these conditions, and I therefore decided to ask the patient to consent to this treatment, explaining to him that it had never been in use for this purpose before, but that I had reason to believe it might succeed. As he had by now come to realize the formidable nature of his complaint and the limitations of our resources, he agreed to the experiment. Nevertheless, it was not without some hesitation that I arranged for an inoculation with malarial blood on April 4, 1934. This inoculation was successful, the reaction reaching a peak of 105° F. on April 15 and 16, and

finally being checked after some eight days by quinine treatment. The effect on the eruption was remarkable. As the fever reached its maximum both the tumours and the pre-mycotic areas melted away, leaving a skin almost normal in appearance. Seemingly the experiment had been a success. It soon, however, became evident that the improvement was not to be completely maintained, for in a lesser but nevertheless definite degree the tumours and pre-mycotic areas gradually returned. Here, nevertheless, was at least enough to warrant a second inoculation, which took effect on July 12, the artificially produced malaria being permitted to follow a course of some twelve days, accompanied by high fever and rigors. A repetition of the previous course of events was noted—i.e., a clearing up of the eruption and then some recrudescence. Nevertheless, by these two treatments the degree and extent of the disease had been so much reduced that it was now possible to resume x-ray therapy, and by it to arrest and check the now relatively small amount of eruption. It is interesting to record that in November, 1934, an intravenous injection of pyrifur was made, producing a temperature of 101.4° F. The result was disastrous: considerable new erythematous patches developed, and the original mycotic lesions were all aggravated, some days elapsing before the skin readjusted itself to its previous state. This experiment suggests, if no more, that it was not the fever as such but the underlying disease process, of which the fever was a symptom or reaction, that brought about the improvement; which may remind us of the distinction between artificial protein shock and the very complex reactions of a natural morbid process such as erysipelas or malaria.

Third Admission : April 8, 1936, to August 5, 1936

The period following the second discharge from the skin wards in December, 1934, up to November, 1935, can be described as one of comparatively good health. Then a deterioration set in. Severe backache was experienced, with vomiting and progressive anaemia. The spleen was considerably enlarged and there were palpable glands in the right axilla. All these symptoms could seemingly be accounted for by earlier conditions—the splenic enlargement being attributed to what was supposed to be the recurrent malaria, the enlarged glands to a neighbouring patch of affected skin, and the anaemia to the prolonged radiotherapy. On admission to a medical ward on April 8, 1936, the patient was pale and looked very ill. He complained of epigastric discomfort, occasional vomiting—not related to food—backache, and loss of weight. Of the previous extensive eruption there now remained only a dry patch over the right scapula and two small patches on the legs. The liver, spleen, and a group of glands in the right axilla were all enlarged. For some fifteen weeks there was present an irregular pyrexia up to 100° F., with occasional rigors. Blood counts made on several occasions showed an anaemia which persisted in spite of haematinics such as iron and liver. There was no evidence of haemolysis and no reticulocytosis. No malarial parasites were observed. The white cell count disclosed a leucopenia with a normal differential count. The absence of an eosinophilia calls for comment. On discharge from hospital on August 5, 1936, the patient is reported to have said that he felt quite fit, and his weight, which had fallen to 8 st. 7 lb., had then reached 10 st. 4 lb.

Fourth Admission

The fourth and last phase includes a period between re-admission on September 22 and the death of the patient on November 19, 1936. The recurrence of the abdominal pain with rigors and pyrexia, the enlarged glands, liver, and spleen, together with other signs and symptoms, if not unquestionable, were at least favourable to the diagnosis of Hodgkin's disease, and this was supported by the microscopical examination of a lymphatic gland removed on October 7, 1936, which showed loss of structure, diffuse fibrosis, endothelial proliferation, and occasional giant cells of the Hodgkin type. Although there were no eosinophils Dr. Scarff reported that the appearances were strongly suggestive of Hodgkin's disease. Throughout the fourth admission the general condition steadily worsened. Ascites developed, there was pronounced anaemia with a leucopenia, the white blood cells dropped to 2,800 per c.mm., and a fall of blood pressure and progressive weakness terminated in death on November 19, 1936.

Necropsy (Bland-Sutton Institute, 231/36)

The following is abstracted from the post-mortem report:

"The right pleural cavity contained one pint of clear straw-coloured fluid: there were dense pleural adhesions over the surface of the left lung. The heart weighed 8 oz., and was wasted, although the muscle was firm. There was an ulcer measuring 1 inch by 1/2 inch in the oesophagus at the level of the bifurcation of the trachea. Deposits of a firm white growth were present in the upper lobe of the left lung, in the spleen, and in the liver. Those in the lung and spleen measured up to 1 1/2 inches in diameter, whereas those in the liver were larger, some having a diameter of 2 inches, umbilication occurring in the superficial tumours which projected above the surface of the liver: the spleen and liver were both enlarged, the former weighing 27 oz., the latter 116 oz. There were three pints of clear fluid in the peritoneal cavity. A section of the femur showed the upper three-quarters of the shaft filled with red marrow. Histological examination of the white masses showed proliferation of cells with large clear nuclei resembling reticulo-endothelial cells. There were also numerous giant cells exhibiting two or three darkly stained nuclei. Although only a few eosinophils were present, the appearances were those of acute Hodgkin's disease rather than a reticulum-celled lymphosarcoma."

Commentary

The illness and death of this patient, as recorded above, have served to throw some light, if in no more than a relative and small way, on the pathology and therapeutics of an obscure skin disease. Expressed in their simplest terms the facts are these. The patient developed first the characteristic lesions of mycosis fungoides: he was brought before the Dermatological Section of the Royal Society of Medicine on May 17, 1934, and again on December 19, 1935, the diagnosis being accepted by all those present on both occasions (MacCormac, 1934, 1936). As the result of malaria therapy the extensive eruption was finally reduced to three small patches, as noted on the third admission (April 8, 1936), being subsequently and up to the patient's death in November, 1936, negligible or absent. This introduced a new therapeutic principle. Further, the terminal transformation in this case of what was at first mycosis fungoides into what became Hodgkin's disease seems to establish the unity of these two clinical entities, a relation that has often been suggested. If the evidence in this case is considered good enough to establish this relation, then it follows that there is an aetiology and pathology common to both these forms of reticulo-endotheliosis. Nevertheless, as Sir Humphry Rolleston (1924) has pointed out, in the usual run of cases of Hodgkin's disease the changes are confined to the lymphoid structures—namely, the lymphatic glands, spleen, walls of portal vessels—and in the interstitial tissue of the lungs, kidneys, bone marrow, subcutaneous tissue, and serous membranes. Lymphadenomatous nodules in the skin are of extremely rare occurrence. Sir H. Rolleston had been able to collect only twelve cases in 1924: such nodules, I would venture to suggest, are in the nature of metastases. Since mycosis fungoides similarly keeps to its own territory, only rarely invading the deeper tissues or viscera, it would seem that the hypothetical virus has a sort of selective affinity for different parts of the reticulo-endothelial systems. Nevertheless the cure of the skin disease in this case did not prevent the subsequent development of a progressive and fatal form of reticulo-endotheliosis elsewhere. In another field—namely, that of micro-anatomy—there is to be obtained further support for the identity of mycosis fungoides and Hodgkin's disease, and in this connexion Civatte's (1936) authoritative observations in the *Nouvelle Pratique Dermatologique* may be quoted as follows:

"In lymphogranulomatosis and mycosis the infiltrates show a greater variety (as compared with the infiltrates of leukaemia).

Polynuclear neutrophils and eosinophils—and the latter sometimes in great abundance—lymphocytes, plasmocytes, and all the other polyblasts, are met with there in proportions which vary according to the case. But there are always a considerable number of large histiocytes with a voluminous nucleus and poor in chromatin, with a homogeneous and faintly basophil cytoplasm: sometimes these cells undertake the office of macrophages; they are thus genuine histiocytes. Here and there one of these cells is provided with a budding nucleus, and recalls a Sternberg cell; it is a transitional form. Sometimes even a true Sternberg cell is met with, identical with those which are seen in abundance in the glands in Hodgkin's disease. The diagnosis of cutaneous lymphogranulomatosis will be made if the clinical type is not clearly that of mycosis. But it must be realized that the most characteristic mycosis will also sometimes show genuine Sternberg cells. The microscope cannot, thus, distinguish between the two affections. Moreover, it is not certain that these are two different diseases: mycosis is perhaps only a special clinical type of lymphogranulomatosis, a pure cutaneous lymphogranulomatosis. It is known, moreover, that in certain cases an 'adenitis' appears in the terminal stages of the evolution of mycosis: the primarily cutaneous lymphogranulomatosis has invaded the glands."

Many authorities are prepared to go much further, creating a single and comprehensive group, the lymphoblastomas, embracing conditions both simple and malignant, such as lymphoid leukaemia, Hodgkin's disease, lymphosarcoma, and mycosis fungoides—the type-cell common to all being, according to M. H. Gordon, A. E. Gow, and Sir H. Rolleston (1937), the lymphoblast. The creation of this group relies upon intermediate and transitional forms which are deemed sufficient to link the whole together. The case recorded above serves only to relate two members of the larger group—namely, Hodgkin's disease and mycosis fungoides. From another source I am able to produce some evidence showing that mycosis fungoides is not malignant or cancerous or sarcomatous. In 1919 the late Dr. Henry Beckton, working in the Cancer Research Laboratories in the Middlesex Hospital, demonstrated that when tissue is fixed in weak formol Müller solution, stained with aniline acid fuchsin, and differentiated with picric acid alcohol, the Altmann granules which then appear are profuse in the cells of inflammatory exudates and of simple tumours, whereas they are absent or negligible in the cells of malignant growths. This differentiation is usually so well marked as to be apparent even when the slide upon which the section is mounted is held up against the light and examined with the naked eye, the redness or absence of redness due to the presence or absence of the acid-fast granules being then discernible in many cases. In 1913 the late Dr. J. J. Pringle brought a patient with mycosis fungoides before the Dermatological Section of the Royal Society of Medicine. In this case I had found giant cells (Sternberg cells) and had provided Dr. Beckton with tissue, which he prepared as described above and in which the Altmann granules were demonstrable in the cellular infiltrate in abundance. This, so far as it goes, favours the non-malignant nature of mycosis fungoides and, by inference, of Hodgkin's disease also.

In putting together the above record I have drawn upon the reports and clinical notes of my colleagues in the medical department and the Bland-Sutton Institute of Pathology, who have generously permitted me to make use of them. I am under an especial debt to Dr. Arthur Willcox, who when medical registrar had collected much of the material upon which this paper is based, and with whom, had circumstances permitted, I had hoped to collaborate.

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