SARCOIDOSIS

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In 1875 Jonathan Hutchinson made the following description of a case of cutaneous sarcoid :—

‘ On the front of his legs, some of his fingers and on one forearm, were a number of patches consisting in the first instance of distinct tubercles, which afterwards became confluent and then lost their tuberculous character. The patches were peculiar chiefly on account of their dark purple colour ; this tint seemed to depend partly upon venous congestion and partly upon deposit of colouring matter in the tissues, for although their margins could be made pale by pressure, no amount of squeezing altered the colour of the central parts. The patches were irregular in size and shape, distinctly raised above the general surface, their margin for the most part irregular and abruptly defined, and their surface smooth and almost glossy, or sometimes covered with thin dry epidermic scales. Their elevation above the surrounding skin was due in great part to oedema, for they could be made to pit by continued pressure and, in fact, could be squeezed until all thickening disappeared. They were neither tender nor painful. The skin around them was slightly oedematous.’

This is probably one of the earliest records of the disease and Besnier (1889) referred to this description of Hutchinson’s and identified the lesion as those of lupus pernio, when writing his own original article describing this condition.

In 1899 Boeck described the cutaneous lesions and microscopical structure of a distinctive skin affection to which he applied the term ‘ Sarcoids of the skin ’ thinking them to be due to an infiltration of the skin by a leukaemoid tissue.

For many years Boeck’s ‘ benign sarcoids ’ were regarded as purely a dermatological condition. In 1914, J. Schaumann demonstrated that Boeck’s sarcoid and lupus pernio were histologically the same disease. Later he demonstrated that there were associated visceral lesions showing the same histological picture and developed the theory that the cutaneous lesions were but one manifestation of a generalized systemic affection.

Since this time, this disease entity has received a much wider recognition and much has been added to our knowledge of the subject by the many case reports which have been published. Many and varied are the distributions of the lesions, and it is now realized that there is no organ of the body which may not become involved, and that it no longer can be regarded as a comparative rarity only to be encountered at dermatological clinics.

Pathology

The histology of the sarcoid lesion forms a well-recognized microscopical picture. It consists of a collection of pale staining epithelioid cells among which giant cells of the Langham’s type are frequently to be seen. Lymphocytes in small number are present at the periphery. The diagnostic features which differentiate this from other similar tissue reactions are as follows :—(1) The absence of any tendency to caseation, this feature being responsible for the term ‘ hard tubercle.’ (2) The absence of tissue reaction around the tubercle. (3) A tendency to hyalinization in the older nodules. (4) The absence of acid-fast bacilli in the lesion. This distinguishes the microscopical picture from the hyperplastic form of tuberculosis. The typical

appearances of the histology of sarcoidosis is well illustrated in Figures 1 and 2.

The post-mortem appearances will depend largely upon the clinical form which the disease has taken. The cutaneous lesions are not obvious on superficial examination although some pigmentation of the skin may remain after death. Enlargement of the parotid, sub-maxillary, sublingual and lachrymal glands is a prominent feature in some cases. Superficial lymph nodes are frequently affected although the enlargement may be insignificant. Nodules of sarcoid tissue are occasionally to be found in the mucous membrane of the mouth, throat and nose. The tonsils are very frequently involved and tonsillar biopsy forms a useful means of diagnosis where there is no obvious lymph node enlargement. This has the advantage of being safer than the practice of liver puncture which has been advocated.

In the thorax the most striking changes will usually be found in the hilar glands which become considerably enlarged and which by bronchial compression may cause atelectasis of one or more segments of the lung. If the lungs are involved they usually present a finely striated appearance due to the involvement of the perilobular lymphatics and the presence of a fine reticular fibrosis. Nodules are occasionally found involving the myocardium and pericardium.

Splenic enlargement commonly occurs and some degree of hepatomegaly is usually present. Enlargement of the mesenteric lymph nodes can be seen and cases have been described where involvement of the intestine itself has occurred. Gore and McCarthy (1944) report a case in which the stomach showed typical changes and it has been known to produce an appearance closely resembling Crohn's disease in the terminal ileum, Watson, Wagenstein et al. (1945), A. Morland (1946).

In the central nervous system the most frequent regions to be involved are the pituitary gland and the interpeduncular fossa.

Evidence of inflammation of the uveal tract may be seen in the presence of keratic precipitates in the anterior chamber of the eye and thickening of the ciliary body.

The bone marrow is infrequently involved but where this does occur there may be some malformation of the phalanges of the fingers

and toes. In such cases section of the bones will show cyst-like areas which on microscopy prove to be filled with typical granulomatous tissue. Because of this involvement of the marrow, sternal puncture may establish the diagnosis during life. As will be seen from the foregoing, sarcoidosis is a generalized systemic condition in which the lymphoid tissue is predominantly involved and it is true to say that there is no organ of the body which may not show macroscopical or microscopical evidence of the disease.

Clinical Features

Clinically sarcoidosis pursues a prolonged and benign course. The disease commences as a rule in young adult life, most cases developing symptoms before the age of 35. In a series of 200 cases collected by Kissmeyer (1931) half the cases developed under 30 years of age.

The disease is usually monosymptomatic at its commencement, but with the passage of time manifestations of its more widespread nature tend to develop. Some cases, however, remain monosymptomatic throughout their course. Fever and general constitutional disturbances are not common features of Boeck's sarcoid, most patients being afebrile and only occasionally a temperature recording as high as 100° F. is encountered.

Although carrying a low mortality rate, death may ensue. This most frequently results from cardiac failure secondary to the widespread fibrosis which may occur in the lungs. Direct involvement of the heart itself may give rise to a similar termination.

Involvement of the central nervous system may also give rise to a fatal termination. A case reported by Reis and Rothfeld (1931) showed involvement of the brain and death resulted from a series of epileptiform attacks.

Death can occur from the development of active tuberculosis, an interesting feature in view of the similarity of the histology and the theories connecting the aetiology of Boeck's sarcoid with the tubercle bacillus. Schaumann holds the view that this is often a cause of death.

The most frequent clinical findings are encountered within the thorax, next peripheral lymph node involvement, followed by skin

Low power view of lymph gland involvement.

High power of previous section showing epithelioid cells and giant cell.

Glandular enlargement alone.

Glandular enlargement with radiating fibrosis.

Glandular enlargement with diffuse fibrosis in lung fields.

Nodular type of Pulmonary Sarcoidosis.

lesions, ocular manifestations and alterations in the bones. Other organs are less frequently involved.

Thoracic Manifestations

Pulmonary lesions are among the most common to be encountered in this disease, and Longcope records 29 out of his 31 cases having shown radiological evidence of pulmonary sarcoidosis. Symptoms only occur in a relatively small proportion of cases, and the diagnosis will depend upon routine radiological examination whenever there are other signs suggesting a diagnosis of Boeck's sarcoid.

The radiological appearances fall into five groups:—

1. Bilateral hilar glandular enlargement, without parenchymal opacities.
2. Hilar gland enlargement with strand-like processes radiating from the increased root shadows.
3. Miliary type.
4. Nodular infiltration.
5. Diffuse and confluent infiltration.

Figures 3-6 illustrate some characteristic examples.

The radiological appearances are in no way pathognomonic of the disease and have to be differentiated on clinical grounds from such conditions as erythema nodosum, rheumatic pneumonitis, eosinophilic infiltrations, other forms of lymphadenopathy and the pneumoconioses (Berstein and Sussman (1945)). The miliary type closely resembles tuberculosis and it is possible that some reported instances of 'healed miliary tuberculosis' of the lungs were, in fact, cases of pulmonary sarcoidosis.

Dyspnoea is the commonest symptom encountered in the pulmonary form of the disease. This is often slight, but Isbister (1945) records a case in which bilateral spontaneous pneumothorax occurred, and Snapper (1938) states that in one of his cases enlargement of hilar glands gave rise to extensive atelectasis. One case observed by the writer presented itself as a case of left sided chest pain.

Despite the very evident radiological appearances physical signs are negligible except in such uncommon cases as mentioned above.

The prognosis in these cases is good. King (1945) reports a clearing of the lesions in 60 per cent. of cases within a period of three years. Death, when it does occur, may result from right heart failure due to extensive pulmonary fibrosis, or as the result of the development of active pulmonary tuberculosis.

Invasion of the myocardium and pericardium is reported in a series of 28 autopsies (Berstein (idem)). There is usually little clinical evidence of such involvement although arrhythmias, conduction defects and myocardial failure have been mentioned.

Glandular Form

Reference has already been made to the frequent involvement of the hilar glands in sarcoidosis.

The more peripherally situated lymphatic glands are also found to be enlarged in a considerable number of cases, such enlargement may be slight or gross, and glandular biopsy is the usual method of establishing the diagnosis.

The glands are discrete and firm, and it is the cervical group which is most often to be found the site of election, especially when the glandular lesions are of the localized form.

Occasionally a generalized lymphadenopathy is encountered, when the axillary, inguinal and epitrochlear glands become implicated. Reference here must once more be made to the fact that the tonsils commonly show evidence of the disease although no gross clinical signs may be detected, and section will often give conclusive proof of the nature of the disease. Not only are the lymphatic glands of the neck enlarged, but the salivary and lachrymal glands may also take part in the clinical picture. With such enlargement of the lachrymal, parotid and submaxillary glands one form of Mikulicz's syndrome may be seen. Disease of the parotids alone may give rise to a mistaken diagnosis of mumps.

Ocular symptoms and signs accompany or precede salivary disturbances in a number of cases and this will be referred to in the section dealing with such lesions.

In the abdomen, splenomegaly and mesenteric lymph node enlargement are encountered and the diagnosis may be confused with Hodgkin's disease or tuberculosis.

Ocular Manifestations

Corneal lesions, when present, take the form of an interstitial keratitis. Iritis and iridocyclitis are also to be encountered as a sign of sarcoidosis of the uveal tract, and in conjunction with other lesions are a useful diagnostic pointer.

The writer was able to establish a diagnosis of sarcoidosis over the telephone when a patient stated that she was suffering from her second attack of 'mumps' in two years and that she had not enjoyed good health since a similar attack three years previously.

The combination of swelling of the parotid glands together with ocular symptoms indicating an inflammatory lesion of the uveal tract, is a well recognized syndrome to which the name of uveoparotid fever has been given. It is a condition with which the name of Heerfordt is justly linked since it was he who drew attention to the combination of these lesions.

Cutaneous Lesions

The dermatological manifestations of Boeck's sarcoid have attracted the greatest attention, and the greater part of the literature upon the subject deals with the skin lesions.

The commonest type of lesion is the chilblain type, *lupus pernio*. The nose, cheeks, ears and forehead become involved in a process which produces violaceous indurated patches, which can be made to blanch on pressure and then reveal the small yellowish nodules which suggested their lupoid character. The areas involved usually show well-defined margins which, when central involution occurs, gives the lesions a ring-like appearance. Other forms include a *miliary type* which consists of multiple small nodules situated about the nose, cheeks and lips; and coalescence of these nodules may give rise to actual *tumour* formation of the type described by Boeck.

This nodular form may closely resemble leprosy and will then produce great disfigurement of the features. The commonest situation of the lesions has already been mentioned, but in addition to these regions, the outer surface of the arms and shoulders may be involved and more rarely the trunk.

When the trunk is implicated the lesions frequently take the form of deeply indurated *plaques* with well-defined raised margins.

Healing eventually occurs, and usually leaves no trace, or there may be some slight residual scarring or atrophy of the skin.

Osseous Lesions

The bone marrow may become infiltrated by epithelioid cells and giant cell systems. As a rule there is no clinical evidence of this occurrence, radiological changes alone being demonstrable. The commonest site of these lesions is in the phalanges of the fingers or toes. The radiological appearance is characteristic and may be of great value in establishing the diagnosis in cases of doubt. Small, well-defined punched-out areas may be seen in one or more of the phalanges, metacarpals or metatarsals. These are frequently single, but more than one such lesion may be seen. There is also described a more generalized lattice-like alteration in the pattern of the cancellous bone.

At times the infiltrated area may be sufficiently large as actually to expand the cortex of the bone, and it is important to note that there is no evidence of periosteal reaction.

In this latter type of case deformities of the digits tends to occur. The skin is often discoloured being purplish in hue, and there is thickening of the skin, producing a swollen appearance of the fingers or toes similar to that seen with true chilblains. The finger-tips are often square-ended and some dorsiflexion of the terminal phalanx may be seen, and there may be later even some loss of substance. The fully developed lesions were admirably described by Jungling (1921) to which he gave the descriptive term '*Osteitis tuberculosa multiplex cystica*.'

Where skin changes accompany the phalangeal swelling there is a very close resemblance to tuberculous dactylitis.

Gastro-Intestinal Lesions

Involvement of the intestinal tract by sarcoid tissue is extremely uncommon but there is at least one confirmed case of sarcoidosis of the stomach which has been reported, Gore and McCarthy (1944). Lesions within the

small intestine have given rise to some speculation. The question as to whether 'regional ileitis' is a manifestation of 'Boeck's sarcoid' is not as yet settled. Snapper and Pompen (1938) in their monograph upon regional ileitis maintain that there is no link between the two conditions, since they had never seen a case of sarcoidosis with intestinal involvement nor had they seen a case of ileitis showing other features of sarcoid. Against this objection is Morland's case (1947) in which regional ileitis occurred in a patient showing the typical radiological changes of sarcoidosis of the lungs. In addition to this Watson, Rigler, Wagenstein and McCartney (1945) report a case of sarcoidosis of the small intestine simulating ileojejunitis. Undoubtedly there is extreme similarity in the histological picture of the two conditions and it is of interest to note that Williams and Nickerson (1935) report a positive skin reaction to an emulsion of sarcoid tissue in one case of 'regional ileitis.'

Central Nervous System

Invasion of the central nervous system by sarcoidosis is extremely uncommon, but several examples have been recorded. The pituitary body and interpeduncular fossa seem to be the region of choice, and in the pituitary itself it would appear that the pars posterior is the more usually damaged, diabetes insipidus resulting from such a lesion.

The case of Reis and Rothfeld has already been referred to in which death resulted from epileptiform attacks; here a tumour-like mass was found upon the optic nerve.

An unusual case was reported by Lewis (1941) in which Adie's Syndrome occurred in a case which later showed generalized manifestations of sarcoidosis.

Facial palsy resulting from interruption of impulses along the seventh cranial nerve is occasionally seen when the parotid gland becomes enlarged. Bilateral facial paralysis of the lower motor neurone type occurred in the case already mentioned who suffered from recurrent 'mumps.'

Blood Changes

Blood changes are often absent, although a monocytosis is stated to be the change which is

most often seen if the blood picture is abnormal. Longcope and Pearson (1937) in their series of cases, record an eosinophilia rising to 35 per cent. in one instance and in yet another case record 7 per cent. of eosinophils.

Perhaps one of the most striking alterations which has been noted by several observers is the presence of a hyperprotinaemia. Figures in the region of 8-9 gms. per cent. are quoted, and it is the globulin fraction which shows the greater relative increase, although a rise in the level of albumin resulting in a similar elevation of the total proteins has also been recorded.

The sedimentation rate is variable, abnormal figures being encountered chiefly in those cases in which the albumin-globulin ratio is altered.

Diagnosis

The diagnosis of Boeck's sarcoid is not usually difficult, provided that the condition is born in mind as a possible cause of lymphatic enlargement, or in cases where the radiological appearances suggest pulmonary tuberculosis in the absence of the usual symptoms.

The most useful diagnostic pointer is the demonstration of a negative tuberculin reaction to all dilutions, and this should suggest the need for microscopical examination of any available tissue; be it the result of glandular, tonsillar or liver biopsy, or the examination of marrow smears.

The hyperproteinaemia when present, particularly with an absolute increase of the globulin fraction is valuable additional evidence.

The Scandinavian observer, Kweim (1941), used an emulsion of sarcoid tissue as an antigen for an intracutaneous test. The results obtained appeared to show a high degree of accuracy in confirming the diagnosis. A positive reaction to the intracutaneous test, consisting of an indolent erythematous area occasionally ulcerating, was obtained in 12 out of 13 established cases. The reaction was negative in all controls. The slight disadvantages to the use of this test lie in the persistence of the positive reaction and in the delay occurring before a positive result may appear.

A series of cases investigated by Danbolt and Nilssen (1945) showed a definite positive result within two weeks in 30 of their 34

positive reactions, and out of 36 established cases of sarcoidosis they showed an incidence of 94.5 per cent. positive reactions.

Aetiology

The discussions centering around the underlying cause of the lesions now recognized as forming the essential pathological picture of sarcoidosis have been varied, but so far inconclusive. The difficulty which has presented itself is the similarity of the cellular reaction in this specific disease to many other granulomata, and the inability to either demonstrate a specific causative organism or to transmit the disease to the experimental animal.

Tissue reactions such as have been described in the pathological section, may be produced by a variety of foreign agents including inanimate substances of a fatty nature. In certain respects the tubercle bacillus evokes such a response, in leprosy a very similar histological picture may be seen and there are some adherents to the view that these last two conditions are closely related, Kissmeyer (1932), Kissmeyer and Nielsen (1933).

Attention has been drawn to the close similarity to Hodgkin's disease, hence the term 'lymphogranuloma Benigna' of Schaumann. Indeed Hadfield and Garrod (1942) consider this condition in close relationship to the endothelioses.

However, the relationship of this disease to infections with the tubercle bacillus has excited the greatest controversy. The results of clinical and pathological investigations have certainly shown a very strong link between the two.

The similarity of the histology is but one feature which stresses this, and the high incidence of negative reactions to one or other test for tuberculin sensitivity it seems cannot be due to chance alone. This has been held to be due to a state of 'allergy' by several observers. (Boeck, Schaumann, Jungling and others.) In further support of the allergic theory are the results observed by Lemming (1940) when he failed to convert his cases of sarcoid to a positive tuberculin reaction with B.C.G.

Strengthening these conclusions are the observations that the skin lesions of sarcoid tend to resolve where active tuberculosis has

developed, and in the development of tuberculosis as a terminal event in many cases. This latter claim of Schaumann has not been confirmed by other authorities.

Against the tuberculous hypothesis is the inability to demonstrate the bacilli in the lesions or to transmit tuberculosis from the lesions by animal inoculation. On the other hand Schaumann (1934) holds the view that single inoculation is insufficient to demonstrate the bacillus and maintains that several re-inoculations through a series of animals are necessary, owing to the tubercle bacillus having become converted to a filterable form.

It is indeed difficult to correlate these two conflicting views upon the aetiology of this condition. There are, however, the results of two separate experimental studies which may be considered to supply an answer to some of the discrepancies in the foregoing hypothesis.

Firstly there are the interesting results obtained by Sabin, Doan and Forkner (1930) when observing the tissue reactions of animals to the lipoids of the tubercle bacillus. A phosphatide fraction was demonstrated to be very active in producing an exudation of epithelioid cells and giant cell formation. Reference has already been made to similar reactions produced by other fats and oils.

Secondly, must be mentioned, the work carried out by Rothchild, Friedenwald and Berstein (1934) upon desensitization of animals to tuberculin after infection with tubercle bacilli.

The object of this work was to observe whether the exclusion of the allergic factor in any way influenced the course of the disease. In connection with the present study, their observation is of the greatest interest that under these circumstances the lesions were harder and showed much less tendency to caseation.

Can it be that the characteristic lesions of sarcoidosis result from bacterial moieties rather than from the bacteria themselves?

Many of the observed features of this disease can be explained upon such an hypothesis. The high incidence of tuberculin negativity would point to a process of natural desensitization, similar to that carried out by Rothchild and would also conform to the observation that in these cases a history of contact with active tuberculosis is extremely

rare. Under the latter conditions, massive infection with tubercle bacilli would occur early and there would be no opportunity for a process of "desensitization" to take place. Sabin's work shows that such a lesion may be produced by fractions of the tubercle bacillus and if the lesions of sarcoid were due to such 'fractions' it would naturally follow that no organisms could be demonstrated.

The one great objection to the view held by Schaumann, who maintains that these lesions are the result of invasion of the body by tubercle *bacilli*, are the completely negative bacteriological investigations.

The inability of Lemming to produce a state of sensitivity with B.C.G., also tends to

support the view that there is a pre-existing state of desensitization in these cases.

It has been suggested that there may be a different aetiological factor in some cases of Boeck's sarcoid, since a positive Mantoux reaction is occasionally found, but it must be born in mind that later infection with tuberculosis may occur and under such circumstances a positive reaction would not be surprising.

Many have been the theories put forward to account for the causation of this interesting clinical condition, but at the present moment one may say that a satisfactory explanation is not forthcoming and one can only conclude that here is yet another medical mystery whose perpetration must be laid at the door of an 'unknown virus.'

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