GRANULOMATOUS ORCHITIS

WITH REPORT OF A CASE

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Granulomatous lesions of the testis are rare. The case to be described is of interest, clinically in that it closely mimicked a testicular neoplasm, and pathologically because of the difficulty in arriving at a definite diagnosis. A provisional rapid section was first considered to show tuberculosis of the testis; on further consideration the histological appearances were regarded as being consistent with sarcoidosis; perusal of the literature finally raised the question of granulomatous orchitis.

The concept of sarcoidosis is still considerably confused and, indeed, there are doubts whether it should be regarded as an entity (Scadding[1]). The histological appearances in this case certainly resemble those of sarcoidosis very closely. However, the fact that the experimental injection of certain acid-fast lipid fractions of human spermatozoa can produce granulomatous lesions very similar to that seen in this case (Berg, 1954[2]), makes one hesitate to apply the label of sarcoidosis without further reservation.

CASE REPORT

C.W.B., a labourer aged 58 years (hospital ref. no. R. I. 207035/55), was admitted to the Churchill Hospital, Oxford, in May 1955, under the care of Mr. A. S. Till. Two months previously he had noticed an aching and a heavy feeling in the left testis. In the course of a few days the testis had become enlarged, and after that, in the patient's opinion, it had varied in size to some extent. There were no other symptoms at all. In the patient's past history there was a story of two operations to his hip at the age of 11 years. The relevant notes were traced, but they gave little information beyond the clinical diagnosis of a tuberculous hip, and that the sinus eventually healed and he was left with a stiff hip.

Examination

The patient looked perfectly well. He was afebrile throughout his stay in hospital. There was no superficial lymphadenopathy. The right testis was normal to palpation. The left testis was about twice the size of the right, smooth and very hard, but retaining its normal shape. Testicular sensation was absent. The epididymis was slightly enlarged, rather hard and nodular, but freely moveable in relation to the body of the testis. The vas deferens was quite normal to palpation.

There was some lack of definition to the right supero-lateral angle of the prostate, but the rest of the gland felt normal. The seminal vesicles were not palpable.

The liver and spleen were not palpable.

There were scars over the left greater trochanter, and the left hip was partially ankylosed.

Investigations

Haemoglobin 97%, 14·4 g. per 100 ml.

White blood-count 4,000 per c. ml. (neutrophils 79%, eosinophils 1%, basophils 1%, monocytes 4%, lymphocytes 15%).

Serum proteins 5·3 per 100 ml. (albumin 3·3 g., globulin 2·0 g.).
Serum acid-phosphatase 4 units.
Blood Wassermann and Kahn reactions negative.
T.B. cultures of 3 early-morning specimens of urine negative.
Mantoux reaction positive with 1/100 old tuberculin.

Radiographs. In the chest old calcified lesions were seen in the left infraclavicular region. No secondary deposits were seen, and no hilar lymphadenopathy. The left hip showed a gross osteo-arthritis with 'the appearances of an old slipped capital femoral epiphysis.' The small bones of the hand showed no cystic changes.

Diagnosis

A neoplasm of the testis, probably a seminoma, seemed to be the most likely diagnosis, in spite of the fact that the epididymis was not quite normal to palpation. The smooth, hard enlargement of the body of the testis, with complete absence of testicular sensation, was quite unlike tuberculosis.

At Operation

The inguinal canal was opened and the cord ligated at the internal inguinal opening. The testis and cord were then removed. The appearance of the testis, after bisecting it in the theatre, did not alter the pre-operative diagnosis of malignant disease of the testis.

Pathological Report

The specimen was reported upon by Dr. W. C. D. Richards as follows (no. 3307/55):

'The specimen consists of a slightly enlarged testis with a portion of spermatic cord. The body of the testis and the epididymis show a diffuse firm, whitish infiltration, but the general shape of the organ is intact.

'*Histology.* A granulomatous lesion affects both the body of the testis and the epididymis (Figs. 1 and 2). In the body (Figs. 1 and 3), except for a few completely atrophied tubules just beneath the tunica albuginea, the supporting cells and the spermatogenic cells of the seminiferous tubules are completely replaced by epithelioid cells and multinucleated giant-cells, which are often arranged so as to resemble tubercles. The outlines of the seminiferous tubules are well maintained, but there is an increase in the reticulin of the basement membrane and of the peritubular interstitial tissues (Fig. 4). The interstitial tissues are infiltrated by lymphocytes and plasma cells, which form a cuff around the granulomatous tubercles.

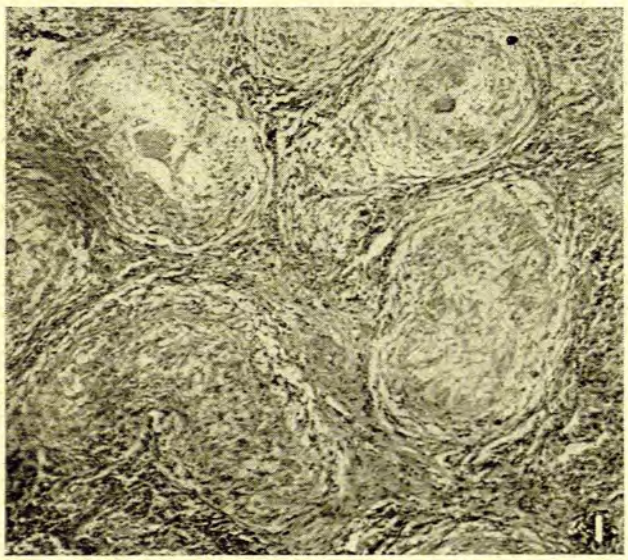

Fig. 1. Low-power view of the body of the testis, showing the tubules to be completely replaced by granulomata consisting of epithelioid cells. Several giant cells are seen. There is no caseation, and appropriately stained sections show no acid-fast bacilli. There is an interstitial infiltration of lymphocytes and plasma cells.

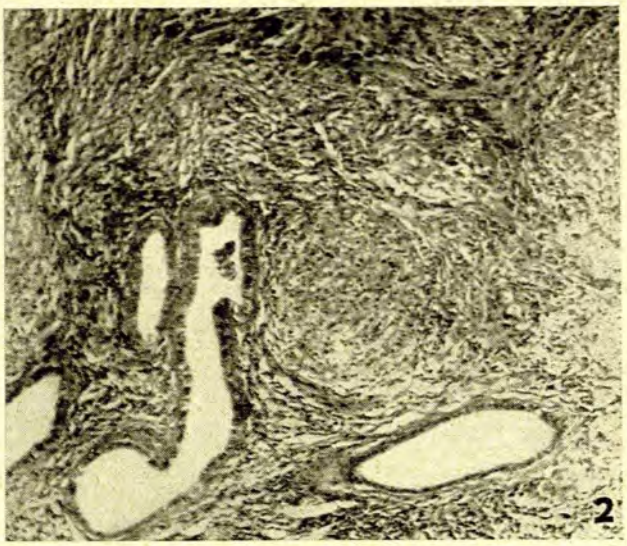

Fig. 2. Low-power view of the epididymis. The granulomatous infiltration is patchy, and more diffuse than in the body of the testis. There is interstitial fibrosis and infiltration by chronic inflammatory cells.

'In the epididymis (Fig. 2) the granulomatous infiltration is patchy, and surrounds degenerating tubules. Some of the tubules contain masses of spermatozoa, around which are macrophages and multinucleated giant cells. Other tubules contain polymorphonuclear leucocytes and macrophages. A few are dilated but free of inflammatory change. There is interstitial fibrosis and infiltration by chronic inflammatory cells but, in contrast to the lesion in the body of the testis, the granulomatous infiltration is more diffuse and, although epithelioid cells are plentiful, giant cells are less numerous. Because of the interstitial character the discrete arrangement of the granulomata observed in the seminiferous tubules is absent.

'Neither in the body of the testis nor in the epididymis is there necrosis or caseation. No micro-organisms can be found in appropriately stained sections. Staining by the method of Berg

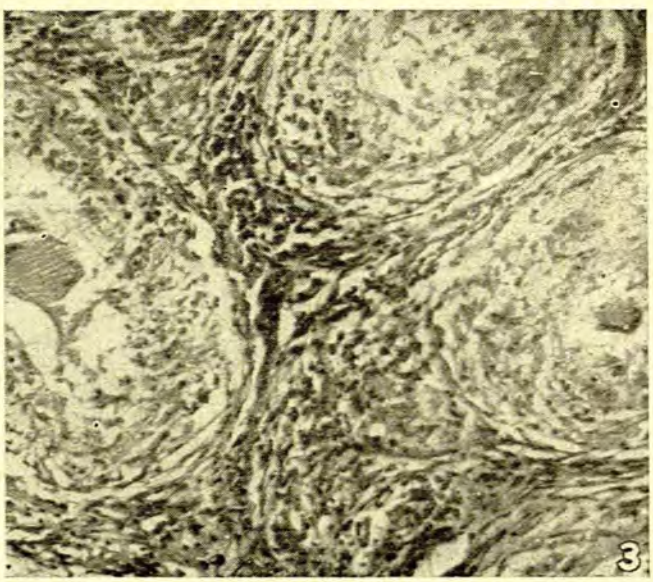

Fig. 3. High-power view of the body of the testis, showing the structure of the granulomata in greater detail.

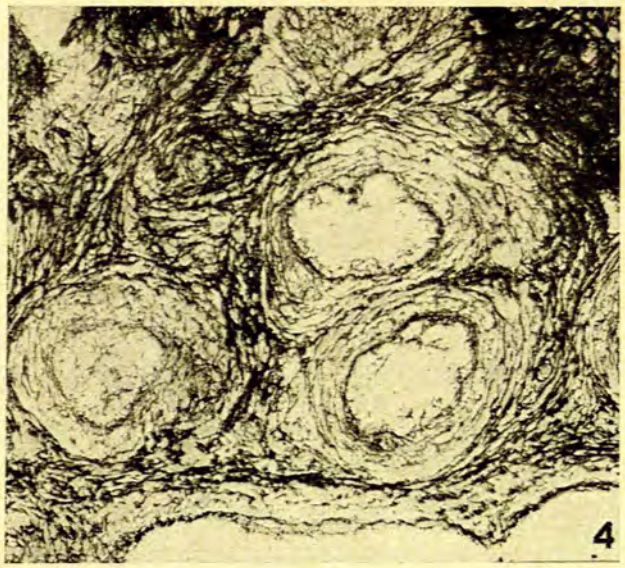

Fig. 4. Reticulin stain of the body of the testis. There is an increase in the reticulin of the basement membrane and of the peritubular interstitial tissue. The strands of reticulin extend into the centre of the granulomata. This is unlike the appearance in tuberculous granulomata, where the reticulin tends to be destroyed.

(1953) fails to reveal spermatozoa or acid-fast material in the body of the testis.

'The appearances are those of a granulomatous orchitis.'

DISCUSSION

The diagnosis in this case would appear to rest between sarcoidosis affecting mainly, if not solely, the testis, and granulomatous orchitis.

For various theories of the aetiology of sarcoidosis reference may be made to the excellent reviews by Cowdell[3] and Longcope and Freiman.[4] The 3 main theories are:

1. That it is a form of atypical tuberculosis.
2. That it is an entity due to a single cause, whether chemical, bacterial or viral, as yet undetermined.
3. That it is merely a tissue reaction to various noxious agents.

Sarcoid-like lesions are known to occur in association with a variety of conditions, including tuberculosis, syphilis, leprosy, leishmaniasis, foreign bodies, and malignant tumours. Chronic exposure to beryllium can give rise to a lesion closely resembling sarcoidosis. It follows that one should exclude all these conditions before diagnosing sarcoidosis. In this case the only condition that needs any serious consideration is tuberculosis, in view of the evidence of tuberculosis in the past both pulmonary and articular. The positive tuberculin reaction is not very signifigant; a considerable proportion of the cases in both Cowdell's and Longcope's series reacted positively.

Most authors have accepted a histological definition of sarcoidosis, in view of the ignorance about its aetiology. According to Longcope and Freiman[4] 'the conclusive demonstration of its presence rests entirely upon the histological structure of the lesions which it produces.' The essential lesions in sarcoidosis are epithelioid granulomata, which are remarkably uniform in appearance, giving a characteristic 'monotony' to the histological pattern. The granulomata do not coalesce. Very characteristic is the absence of caseation and of acid-fast bacilli. In Cowdell's series the rigid application of the latter two diagnostic criteria resulted in the exclusion of no case which in every other way appeared to be sacoidosis. Ricker and Clarke[5] describe the occurrence in 35% of their cases of a fibrinoid necrosis, which is distinguishable from tuberculous caseation, especially by its acellularity. In tuberculous granulomata also the reticulin tends to be destroyed, whereas in sarcoidosis the strands of reticulin can be seen to extend into the centre of the granulomata (Fig. 4). The granulomata may contain giant cells, which however, are not pathognomonic in appearance, and may be of either the foreign-body or Langhans types. Various inclusion bodies in the giant cells, e.g. the Schaumann and asteroid types, have been described in sarcoidosis. They are also found in many other conditions.

Applying the above-mentioned histological criteria, it is apparent how well this case fits the picture of sarcoidosis. One may wonder, however, to what extent the fact that the granulomata are based upon the seminiferous tubules accounts for the regular, 'monotonous' appearance of the granulomata.

Involvement of the testis in generalized sarcoidosis has been described in a few reports, but none is comparable to this case. Nickerson[6] describes one case in which the lesions were few and solitary, and located mainly *in the interstitial tissue*. The liver, spleen and bone-marrow were also involved. Longcope[7] describes a case in a Negro aged 29 years, in which both testis and epididymis were involved, leading to profound changes in the secondary sexual characteristics. Longcope and Freiman[4] mention 2 further cases in a series of 12 autopsies. A search through the literature has revealed no case in which the sole clinical feature was a swelling of the testis.

Apart from the histological criteria, various other investigations may provide supporting evidence in reaching a diagnosis of sarcoidosis, but none offers conclusive proof of the presence of the disease. The tuberculin reaction is frequently negative (60%-70% of Longcope's series) but, as is mentioned above, tuberculin anergy is not an essential requirement for the diagnosis of sarcoidosis. Tuberculin anergy has been used as an argument both for and against the tuberculous theory of the aetiology. There may be an increase in the eosinophils or the monocytes in the peripheral blood, and the ESR may be raised. There may be an increase in the gamma-globulin fraction of the serum proteins. The Nickerson-Kveim reaction, which is the detection, by biopsy, of a sarcoid-like granuloma at the site of intradermal inoculation of a heat-sterilized suspension of human sarcoid tissue, is as yet not of much practical value, for it may take weeks, months, or even a year to obtain a positive result (Longcope and Freiman[4]). The results, however, are

impressive; Siltzbach and Ehrlich[8] record 86% positive results with only 4% false positives.

Consideration of the case presented here thus shows that none of these ancillary methods (the Kveim test was not done) has contributed anything towards establishing the diagnosis.

With regard to the condition described as granulomatous orchitis, the most recent report is that of Spjut and Thorpe,[9] who describe 12 cases. The histological appearances resemble very closely those of the case described here. Small differences are noted. In their series giant cells were seen in only 1 case, whereas they are very numerous in this case. In their series the granulomatous change was in no instance complete. The changes in the epididymis also resemble those in this case; in 5 cases granulomatous lesions were seen which differed from those in the body of the testis in that they were more diffuse and did not have the appearance of being based on the tubular contour; in a further 5 cases there were chronic inflammatory changes but no granulomata.

It is remarkable that Spjut and Thorpe make no mention at all of sarcoidosis in their paper. They do consider the interesting possibility that granulomatous orchitis may be related to the condition known as spermatic granuloma, which occurs in the epididymis.

Spermatic granulomata have been described in several papers (King,[10] Friedman and Garske[11]). Sperm cells, after extravasation into the tissues, disintegrate and liberate an acid-fast lipid fraction, which produces a granulomatous reaction. Berg[2] was able to reproduce this experimentally by extracting this fraction and injecting it subcutaneously into hamsters. The cause of this extravasation is somewhat speculative. Trauma has been invoked as a cause, and cases of injury to the vas have been known to be followed by a spermatic granuloma of the cord (King[10]). Antecedent infection of the epididymis may damage the epithelium, or merely alter the intercellular cement,[10] so permitting the escape of the spermatozoa.

It is difficult to see how this theory can explain the lesion in granulomatous orchitis. Both in this case and in the cases described by Spjut and Thorpe, the granulomata in the body are confined to the tubules. Why should the spermatozoa, on one side only, degenerate *within the tubules* to liberate the lipid fraction which excites the development of the granulomatous reaction. Furthermore, granulomatous reactions are not seen as an aftermath of mumps orchitis, where, in the acute phase, there is extensive breakdown of tubules.

CONCLUSION

It is felt that the case presented is one of granulomatous orchitis. It is evident from the histological sections that the resemblance to sarcoidosis is very close indeed. Points against the diagnosis of sarcoidosis are:

1. The fact that the epididymis does not show quite the characteristic 'monotonous' arrangements of tubercles as seen in the body of the testis, where the appearance may be produced fortuitously by the tubular contours.
2. The fact that, in the few reported cases of testicular involvement in generalized sarcoidosis, there have been significant differences from this case.

On the other hand this case resembles those of Spjut and Thorpe very closely. The only real histological difference is in the number of giant cells observed.

SUMMARY

A case of a granulomatous lesion affecting the testis is described. Clinically it presented as a testicular neoplasm.

The histological appearances of sarcoidosis and granulomatous orchitis are briefly described. It is felt that the most likely diagnosis in this case is granulomatous orchitis, a condition which is being increasingly recognized. The possible relation to spermatic granulomata of the cord is mentioned.

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