RENAL SARCOIDOSIS

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Impairment of renal function in sarcoidosis, although an uncommon finding, can be caused in a variety of ways. The formation of renal calculi is one well-recognized complication (Albright and Reifstein, 1948; Klatskin and Gordon, 1953; Dent, Flynn, and Nabarro, 1953), while nephrocalcinosis is also known to result from the upset of calcium metabolism (Longcope and Freiman, 1952; Shulman, Shoenrich, and McGehee Harvey, 1952; Dent *et al.*, 1953). Less well established is the part played by actual sarcoid infiltration of the kidneys. Although many reports mention lesions in the kidney, the lesions are mostly of limited extent and have generally been considered to be of minor importance (Schaumann, 1933; Garland and Thomson, 1933). A survey of the literature in 1950 by Parker failed to reveal any case in which at necropsy the renal lesions were thought to be the cause of death.

In the reported cases of sarcoid infiltration in which the renal lesions are adequately described they possess the characteristic follicular form (Garland and Thomson; Berger and Relman, 1955). In some cases, confusion results from the coexistence of undoubtedly tuberculous lesions with "endothelioid" follicles considered to be sarcoid (Horton, Lincoln, and Pinner, 1939; Hollister and Harrell, 1941; Ricker and Clark, 1949).

The present case is believed to be an example of sarcoidosis in which the renal lesion was the cause of death, and to show histological changes in the kidneys of a type not previously described in any detail.

Clinical Summary

A man, aged 52, was admitted in coma to Maryfield Hospital, Dundee, on September 26, 1954, and died the following day.

He had been in the hospital six months previously complaining of increasing tiredness, bouts of nausea, and loss of weight (2½ st. lost in two and a half years). At this time the diagnosis of sarcoidosis was made. Radiological examination of the chest showed

hilar enlargement and perihilar mottling; there was iridocyclitis of the left eye, and the Mantoux reaction was negative to 1/100 old tuberculin. The E.S.R. was 27 mm. in the first hour.

Blood pressure was 135/90 mm. Hg; plasma albumin 4.8% and plasma globulin 3.4%. Thymol turbidity was 6 units and cephalin flocculation negative. The blood urea level was 38 mg. per 100 ml. There was albuminuria. Culture of sputum and urine for tubercle bacilli was negative.

Before his second admission to hospital he had been on holiday in Majorca for two weeks. His condition was said to have been deteriorating over the previous few months; he felt ill while on holiday, and, as a result, returned home early. Further deterioration was rapid, and three weeks later he lapsed into coma and was admitted to hospital.

The patient remained in coma in spite of therapy, and died within 24 hours. During this period the following investigations were carried out:

The plasma chloride level was 102 m.Eq. per litre, plasma potassium 7.9 m.Eq. per litre, plasma sodium 163 m.Eq. per litre, blood urea 474 mg. per 100 ml. The CO₂-combining power on September 26 was 1.4 m.Eq. per litre and on September 27 4.8 m.Eq. per litre.

The urine showed albuminuria, granular casts, and red cells.

The blood pressure was 85/68 mm. Hg.

In 1947 the patient had left renal colic, but on investigation only hyperaemia of the trigone was discovered. In 1952 he experienced six weeks' hoarseness. There was an inflammatory lesion of the right vocal cord which cleared spontaneously. In March, 1953, he suffered from subclinical jaundice, and in August had an effusion into the right knee joint, diagnosed as early osteoarthritis. The gradual loss of the sight of the left eye began in January, 1954.

Necropsy

The only external feature of note was a number of small firm nodules in the skin of the left shoulder.

Trachea and Bronchi.—The mucosa was injected and there was considerable haemorrhagic exudate.

Lungs.—The right weighed 750 g. and the left 700 g. All lobes were very congested and oedematous and felt firm and fleshy. Small, spherical, translucent lesions of the size of miliary tubercles were present throughout the lungs. These were most readily seen through the pleura and were most numerous in the interlobar fissures. There was a healed fibrotic tuberculous lesion at the apex of the left lung.

Similar miliary lesions were seen in the liver and spleen. In the spleen (400 g.) the lesions were extremely numerous and in many parts had coalesced to form large white masses.

The lymph nodes, both in the thorax and abdomen, were noted to be enlarged and granular on section.

The kidneys (combined weight 250 g.) were small and of approximately equal size. In both, the cortex was relatively thick and very pale.

Other findings noted were numerous recent petechial haemorrhages in the pons: in the ileum there were five agonal intussusceptions: in the left femur there was a roughly spherical mass of hard calcified material lying in the cancellous bone of the lower end of the shaft, of irregular outline and easily shelled out from the surrounding cancellous bone: the cortical bone seemed normal.

The heart, stomach, pancreas, adrenals, bladder, prostate, testes, and thyroid appeared normal.

Histology

Typical sarcoid lesions are present in the spleen, liver, lymph nodes, lungs, and salivary glands. The lesions consist of solid follicles of "endothelioid" cells with multinucleate giant cells, many of the latter containing cytoplasmic inclusions. Some of these are of Schaumann-body type, but others are clear angular crystalline fragments, of an appearance aptly described as "glass-like." These are doubly refractile and some of the Schaumann bodies also contain doubly refractile material. The follicles show the usual tendency to remain discrete, and there is a most intense collagenous fibrosis in and around these foci. This is best seen in the spleen and lymph nodes. Nowhere is there evidence of caseation.

Lungs.—In addition to the sarcoid lesions already noted, there is oedema of the lungs and a number of alveoli contain masses of fibrin. Many of the smaller branches of the pulmonary arteries show small foci of polymorphonuclear neutrophils infiltrating their walls. Frequently overlying these foci there are small masses of mural thrombus in which there is little organization. There is no

evidence of a necrotizing lesion of the walls, and the only material which stains for fibrin is in the thrombus.

Eyes.—Only the posterior parts of the eyeballs were removed. In the retina of one eye, there are two small *congeries* of mononuclear cells lying in the inner coats and these interrupt the inner nuclear layer. There are no giant cells in these lesions.

Skin.—The lesions noted on the shoulder proved to be an inflammatory acneiform condition.

Femur.—The lesion at the lower end of the femur consists of an irregular mass of structureless calcified material. The appearances are consistent with the radiological diagnosis of a bony infarct.

Kidneys.—Only a few follicles of the usual sarcoid structure are present (Fig. 1). These are mostly found deep in the cortex, and they consist of small aggregates of endothelioid cells, some of which are becoming spindle-shaped. Usually one or two giant cells are present and some of these contain inclusion bodies. As in the other organs these bodies are predominantly of the birefringent glass-like type, but one or two are Schaumann bodies. These "hard tubercles" are not sharply demarcated from the surrounding tissue and are not easily distinguished. One or two have proceeded to fibrosis and contain only a few cells.

As already noted, there are few of these lesions, but there is a very extensive diffuse lesion throughout both kidneys. On low-power examination (Fig. 2), this is seen to consist of an extensive fibrosis of the cortex, which has caused wide separation of the renal tubules. Scattered throughout the fibrous tissue there are many multinucleate giant cells similar to those in the "hard follicles" in the kidney and other organs. In most instances these are not accompanied by endothelioid cells and there is no formation of follicles. Their nuclei are extremely numerous, sometimes arranged peripherally and sometimes forming broad bands across the "waist" of the cell, or scattered diffusely throughout the deeply eosinophilic cytoplasm. Many cells contain large clear vacuoles while a few have a finely stippled appearance (Fig. 3)—the "dust-like" vacuolation described by Ricker and Clark. Again some of these cells contain inclusion bodies which may be glass-like (Fig. 4) or of Schaumann body type, and in addition some have a rounded, somewhat lobulated structure. As in the case of the follicular lesions, many of the inclusions are anisotropic (Fig. 5). In

FIG. 1.—A "hard follicle" of sarcoid in the kidney. Masson trichrome, $\times 200$.

FIG. 2.—Low-power view of renal cortex showing diffuse fibrosis, separation of tubules, and giant cell infiltration. Van Gieson, $\times 73$.

FIG. 3.—Sarcoid giant cell showing extremely numerous nuclei periphery of cell and across its waist, and the "dusty vacuolation" of the cytoplasm. Masson trichrome, $\times 600$.

FIG. 4.—Masses of "glass-like" bodies being engulfed by four giant cells. These bodies are birefringent. Haematoxylin and eosin, $\times 495$.

FIG. 5.—Photomicrograph through polaroid screens showing birefringence of the "glass-like" bodies in a giant cell. $\times 480$.

some instances, a mass of crystalline bodies lying in the stroma is surrounded by several giant cells (Fig. 4). In the von Kossa preparations, some of the Schaumann bodies react positively as for calcium, and in sections stained for elastica both Schaumann bodies and the glass-like crystals stain black.

Occasionally giant cells lie in close apposition to glomeruli and sometimes they form a cuff around an artery (Fig. 6).

A few glomeruli show thickening of Bowman's capsule, but the tufts are not abnormally cellular and there is no apparent thickening of the basement membrane. These changes are no more prominent in those glomeruli which have a closely related clump of giant cells.

The tubules, which as already noted are widely separated by cortical fibrosis, are all rather uniform. They are lined by a low columnar or cubical epithelium and most of them resemble distal convoluted tubules. Only in small areas does one find tubules lined by the tall plump epithelium, characteristic of the normal proximal segment. In some tubules crystalline bodies, mostly anisotropic and similar to those contained within giant cells (Fig. 7), are found lying in the lumen. They are frequently rounded and show radial striation, but some have the appearance of sheaves of crystals and others are of the glass-like type.

In the cortex, some tubules show small deposits of calcium in the von Kossa preparations, but these are not at all numerous, and there is no particular fibrous reaction in their vicinity. Casts—some hyaline, some fibrinous, and others composed of polymorphs—are present in many tubules. A light, rather patchy, interstitial infiltration of lymphocytes is seen in parts of the cortex.

The Prussian blue reaction shows haemosiderin in the fibrous tissue of the cortex. It is distributed focally mostly in relation to granulomas and to isolated giant cells.

Of the intrarenal arteries, only the smaller ones show hyaline thickening of the intima. This is most marked in the interlobar arteries and afferent arterioles and is well developed in the few examples in which arteries are surrounded by giant cells (Fig. 6).

The medulla of the kidneys appears relatively normal and is free from sarcoid infiltration.

In addition to these changes there are several old healed pyelonephritic scars, but none of the lesions described above is found in these scars.

No evidence of amyloid disease was detected in the kidneys, spleen, or liver in sections stained with dahlia and congo red.

Discussion

Sarcoid infiltration of the kidney was described by Spencer and Warren in 1938 and they claim

FIG. 6.—Peri-arterial granuloma with hyaline thickening of the intima. Haematoxylin and eosin, $\times 285$.

FIG. 7.—Crystalline bodies in the lumen of a renal tubule. Haematoxylin and eosin, $\times 710$.

to be the first to describe the lesion. However, Garland and Thomson (1933) report the presence of "non-caseating tubercles" in the kidneys of their case of uveoparotid tuberculosis, a condition which is now accepted as sarcoid. Since then a number of reports have appeared (Longcope, 1941; Chanial, 1937; Berger and Relman, 1955), and in these, with the possible exception of the example reported by Rutishauser and Rywlin (1950), the infiltrating cells have apparently not differed in form or arrangement from those seen elsewhere in the body.

In the present case the diagnosis of the systemic disease is in no doubt. The few "hard follicles" in the kidneys are undoubtedly of sarcoid type and indistinguishable from those seen elsewhere in the body, but the more prominent and extensive renal lesion shows features differing from those seen in the other organs and from those described by other authors. These are the extensive diffuse fibrosis apart from follicle formation, and the distribution within this fibrous tissue of giant cells without their normal retinues of endothelioid cells. However, the giant cells and their inclusions are

similar in every respect to those seen in follicles in the kidneys and other organs, and the whole impression, particularly as seen on low-power examination, is of a diffusely infiltrating granulomatous process, in which the only prominent inflammatory cell is the sarcoid giant cell. This would appear to be an uncommon variant of the usual form of follicular infiltration.

By its very diffuseness it is clear that this lesion would much more readily "strangle" the nephrons and cause renal insufficiency than would the presence of even a very considerable number of the typical localized follicles of sarcoid. It has been said that symptoms in sarcoidosis are the result of mechanical interference with the function of organs (Longcope). While this is not true of the glomerulitis noted by Owen and Henneman (1954) or of Teilum's hyaline glomerular lesions (1951), and is only true indirectly of the lesions of nephrocalcinosis, it may be true of the follicular form of renal infiltration (Berger and Relman) and is almost certainly true of the present diffuse form.

Just how much of the cortical fibrosis and tubular loss is due directly to the granulomatous

process is not clear, but it may be that the granulomatous involvement of intrarenal arteries (Fig. 6) has resulted in endarteritic impairment of the blood supply. The usual result of obliterative endarterial change, as seen for example in nephrosclerosis, is a glomerular fibrosis of a patchy distribution with secondary tubular loss, but here we have a diffuse involvement of the tubules and the peritubular stroma with scarcely any glomerular changes. Since only a few arteries show this granulomatous affection and in view of the diffuse scattering of sarcoid giant cells throughout the cortex, one is forced to believe that this curious lesion is a direct granulomatous infiltration of the cortex.

Impairment of renal function resulting from nephrocalcinosis is reversible, and Dent *et al.* cite one of the cases published by Bjørneboe, Brun, Iversen, Gormsen, and Raaschou (1952) as evidence that nephrocalcinosis itself is reversible. They point out that long-continued elevation of the serum calcium leads to permanent renal damage, so that even if the calcium be reabsorbed one would expect to find a fibrotic kidney, and the lesion under discussion might be interpreted along these lines. However, the small amount of calcium present seems to be a bland deposition and to play little part in the fibrotic process.

This diffuse form of sarcoid of the kidney has not been clearly distinguished previously, although in the case described by Rutishauser and Rywlin the description does approximate to what is seen in this case. There is not much detailed description available of sarcoid infiltration of the kidneys, but if renal biopsy should come into common use (*Brit. med. J.*, 1954) it would be well to remember that in the kidney at least this disease may not

show the easily recognizable follicular architecture which, if not tuberculous, can only be that of sarcoid.

Summary

A case of sarcoidosis is described in which death resulted from renal failure.

The renal lesions of sarcoidosis have in the past been described as infiltration by "hard tubercles," the parenchymal deposition of calcium (nephrocalcinosis), or the formation of renal calculus.

The present case showed an unusual diffuse form of sarcoid granuloma in the kidney which led to tubular loss and renal failure.

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