NON-SILICIOUS ANISOTROPIC CRYSTALS IN TUBERCULOUS SALPINGITIS

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Attention has recently been drawn to the similarity between the histological picture of silicious granuloma and tuberculosis of proliferative type in the Fallopian tube of man (Roberts, 1947). In the differential diagnosis emphasis has been placed on the value of the polarizing microscope. The purpose of the present paper is to draw attention to the presence of doubly refractile, but non-silicious, intracellular, crystalline material in two cases of salpingitis regarded as tuberculous. In one of the cases tuberculous endometritis has subsequently been revealed.

Case Reports

Case 1.—K.C., an unmarried woman of 22 years, complained of pain in the right iliac fossa of several hours duration. She denied any previous abdominal operation, curettage, or tubal insufflation. There was tenderness at the site of the pain, and this was also elicited on movement of the uterus.

At laparotomy on April 20, 1949, the right ovary was found to be enlarged and partly occupied by blood clot the size of a walnut. The right tube was swollen and infiltrated. Partial salpingo-oophorectomy was performed. The left tube and ovary appeared normal. A normal vermiform appendix was removed.

The patient continued to complain of pain in the lower abdomen for a few weeks after operation, but was discharged fit on May 30, 1949.

Pathology.—Of the three separate portions of the specimen, two consisted, respectively, of a narrow piece of ovary 1.5 cm. in length presenting a recently ruptured corpus luteum, and a mass of blood clot of the order of 2 cm. diameter.

The remaining portion of material comprised a segment of swollen Fallopian tube partly covered by loosely adherent blood clot. The fimbriae were not identified. On histological examination all sections of the tube showed a loss of the normal delicate villous architecture. The lumen was reduced in size and contained recent blood clot. The villi were greatly thickened. Within the mucosa, and limited to it, were numerous follicles composed of pale epithelioid cells with prominent multinucleate giant cells. Areas of confluent caseation were demonstrated in the centre of a few of the follicles but only after examination of numerous sections (Fig. 1). Around the follicles there was a wide zone of lymphocytes, and these cells, together with plasma cells, were numerous in the intervening stroma. The giant cells were of both Langhans's and foreign-body types. Within or adjacent to the latter, particles of translucent or pale yellowish material were frequent. These crystalline deposits occurred in aggregations of variable size, but were frequently of the order of 30 μ ; some were considerably smaller, others much larger. No constant crystalline form could be ascribed to them, but only occasionally did they appear acicular. They were strongly doubly refractile (Figs. 2 and 3). They were invariably soluble in dilute (N 1)

FIG. 1.—Section from Case 1 showing caseation. No laminated bodies or anisotropic crystals were present. (Haematoxylin-eosin. $\times 35$).

mineral acids. In parts of the material they were accompanied by a different form of inclusion which appeared as a refractile, but not doubly refractile, concentric laminated body. These bodies were circular, dumb-bell or trefoil ; in size, widely variable but of the order of 50μ . They were to a greater or lesser extent basophilic. Doubly refractile crystals were frequently closely associated with, or actually situated within, these bodies, which were themselves usually enclosed by foreign-body giant cells. Some, however, were extracellular and appeared to have ruptured the containing giant cell. No inclusions were seen in areas showing caseation. Despite painstaking search, acid-fast bacilli were not demonstrated in the numerous preparations examined.

Second Hospital Admission.—Fifteen months later the patient was re-admitted to hospital complaining of left lower abdominal pain and menorrhagia. Her uterus was small, anteverted, mobile, and displaced to the right side. The left tube and ovary were not thickened. X-ray examination of the chest and abdomen were negative. She was curetted on August 30, 1950. The histological picture was that of tuberculous endometritis. The material was cut in serial sections but no inclusions were found. During her stay in hospital the patient developed phlyctenular conjunctivitis.

Case 2.—F.B., a married woman of 22 years, complained of irregular periods associated with pain in the left iliac fossa. She had recently had premenstrual dysmenorrhoea and dyspareunia more to the left on deep penetration. She denied any previous abdominal operation or tubal insufflation but had undergone a curettage following a septic abortion in 1947. She had no family. The uterus was retroverted and pushed to the right, and a tender swelling was present in the left fornix behind the uterus.

At operation on September 27, 1949, a cystic swelling of about 3 cm. diameter was found in the recto-uterine pouch, with adhesions of cartilaginous density between uterus and rectum. Folds of ileum were adherent to the fundus of the uterus. The adhesions were separated and the cyst removed. The uterus was placed in anteversion and the round ligaments shortened.

She had an uneventful convalescence and was discharged fit on October 7, 1949.

FIG. 2.—Section from mucosa of Case 1, lumen to left, photographed by ordinary illumination and through crossed polaroid screens. The numerous well-formed follicles show prominent giant cells. The doubly refractile crystalline material is inconspicuous by ordinary illumination. (Haematoxylin-eosin. $\times 30$).

FIG. 3.—Section from mucosa of Case 1 photographed by ordinary illumination and through partially crossed polaroid screens. This is a higher magnification picture of the upper part of Fig. 1. No laminated bodies are present. All the doubly refractile material shown was acid soluble. (Haematoxylin-eosin. $\times 85$.)

Pathology.—The specimen comprised three separate portions of material. One was a semicircular mass, 2 cm. diameter, consisting of blood clot presenting at one small area on its periphery a boundary zone of lutein cells supported by a narrow rim of fibrous tissue. The second portion consisted of fibrous and adipose tissue together with scanty unstriped muscle fibres. Many transverse sections of arterial wall were distributed throughout, and the tissue was presumed to be part of the broad ligament. Numerous lymph follicles were also present together with a patchy, but at places marked, infiltration by lymphocytes and plasma cells. In the more severely affected areas fibroblastic proliferation with newly formed capillaries was evident. No epithelioid cell follicles, giant cells, or doubly refractile material were present.

The remaining portion of material consisted of fused ovarian tissue and Fallopian tube. The ovarian part of this tissue showed at its peritoneal surface a granulomatous inflammatory lesion. Follicles of pale epithelioid cells were present together with multinucleate giant cells of both Langhans's and foreign-body types. In the granulation tissue intervening between the follicles lymphocytes and plasma cells were prominent, and a similar cellular infiltrate extended for some distance into the ovarian tissue, which was otherwise without significant features. This follicular granulomatous tissue reaction extended to a part of the serous surface of the tubal portion of the specimen. The subserous coat appeared thickened by fibrous tissue and the muscle partially replaced by similar tissue. In both these sites focal round-cell infiltration, mostly perivascular, was present. The lumen contained recent blood. The villi showed marked thickening and fusion, and the normal mucosal pattern was largely destroyed. The mucosa was beset with numerous follicles consisting of a central core of pale staining epithelioid cells with a poorly demarcated peripheral aggregation of lymphocytes and plasma cells: these cells were also prominent in the intervening stroma. Caseation was seen in occasional follicles around some of which concentric fibrosis had occurred. Areas of confluent caseation were scanty. In the greater part of the tube the follicles were non-caseous. Practically all follicles showed one or more multinucleate giant cells of both Langhans's and foreign-body types. The latter frequently, and the former infrequently, presented small intracytoplasmic crystalline inclusions of translucent or yellowish appearance inconspicuous by ordinary illumination but strongly doubly refractile. These crystals were invariably soluble in dilute mineral acids. A concentric laminated type of inclusion was also frequently encountered. These bodies of circular, trefoil or dumb-bell shape were of the order of 50 to 100 μ . Some were pale and inconspicuous by bright illumination, while others showed a strong affinity for haematoxylin and stained positively with the usual methods for demonstrating iron. They were not themselves anisotropic, but were frequently associated with the doubly refractile crystalline material (Fig. 4). These laminated bodies were usually within or adjacent to foreign-body giant cells, but were occasionally found lying free in the collagenous tissue further out in the wall. Tubercle bacilli were not found in numerous suitably stained sections.

Differential Histological Diagnosis

The tissue, in both instances, was received in neutral formalin fixative, and animal inoculation was therefore precluded. Although a careful search was made of numerous sections from each case, acid-fast bacilli were not demonstrated, a difficulty which is, however, widely recognized. The diagnosis rested, in each case, upon the presence of a granulomatous lesion having well-formed follicles, including numerous giant cells and frank caseation in some areas. It is emphasized that the original sections in the two cases showed no suggestion of caseation, and only in the examination of further material were follicles showing central caseation seen. Large areas of confluent caseation were seen in only a very few of the numerous sections.

FIG. 4.—Section from Case 2 showing adenomatous pattern of mucosa and basophilic inclusion of trefoil shape. The intimate relationship of the crystalline material to such bodies is shown in the photograph of the same field through crossed polaroid screens. (Haematoxylin-eosin. $\times 115$.)

It is notable, too, that inclusions were scanty or more commonly absent in relation to the caseous areas, and also that the multinucleate giant cells at the periphery of such areas were mostly of Langhans's type, while those in relation to the inclusions were usually of foreign-body type. Epithelioid cells were prominent in the follicles, whereas in silicious granuloma they are scanty or absent.

The Inclusion Bodies

The anisotropic crystals in each of the cases bore a close morphological resemblance to those of surgical talc. This similarity is emphasized by the frequent occurrence of rounded forms rather than spicules in silicious granuloma of the Fallopian tube (Roberts, 1947). Indeed, in the former of the two cases, the diagnosis of talc granuloma would probably have been made had I not been aware that there was no history of previous operation or other procedure to account for the presence of silica particles in the lesions. The solubility of the crystals in dilute acids established that they were non-silicious in nature: no doubly refractile material was found in numerous sections after acid treatment. The constant relationship of the inclusions to giant cells at once disposed of the possibility of artifact.

The concentric laminated bodies, though refractile, were not birefringent. They were nevertheless frequently closely associated with the anisotropic crystals, a fact that immediately suggested that their relationship was not coincidental. Indeed, many of the concentric bodies examined by polarized light revealed unsuspected enclosed crystals, usually in their centre. It is, however, worthy of note that these laminated inclusions were absent in some of the sections showing numerous crystals. Such a picture was presented in the original routine sections in the first of the cases here described, and the morphological resemblance to talc granuloma was correspondingly closer. Despite their size, the laminated bodies could readily be missed unless the illumination of the field was reduced. Some stood out prominently by virtue of their affinity for haematoxylin. A high proportion stained in whole, or in part, by the usual methods for iron.

It is not, however, the purpose of this paper to discuss the histochemistry of these inclusion bodies beyond the detail necessary to establish their identity with analogous bodies previously reported, and to which reference is made in the discussion to follow.

Discussion

The concentric laminated bodies correspond closely with those described and illustrated by several previous authors, of whom Berg and Bergstrand (1937), Schaumann (1941), Kraus (1942), and Teilum (1949) provide recent full accounts. Schaumann (1917) was the first author to report their presence in sarcoidosis, and they have in consequence been sometimes referred to as "Schaumann bodies." This eponymous term seems unfortunate, in that it tends to imply that they are specific for the sarcoid lesion. Ricker and Clark (1949) report that although they are not pathognomonic for sarcoidosis, they have not been observed in tuberculosis. Rich (1944), discussing their occurrence in sarcoid lesions, maintains that they are never encountered in "unequivocally tuberculous lesions in man or the ordinary laboratory animals." Moreover, bodies apparently entirely similar were described by at least 30 authors during the 60 years preceding Schaumann's description in 1917. Of these,

Bowen (1904), Hektoen (1902), Pelagatti (1901), Rona (1900), and Metchnikoff (1893), provide good descriptions. Lang (1875) is not infrequently accorded priority, but an excellent description and illustration of these bodies is contained in a monograph by Schüppel (1871) dealing with tuberculous lymphadenitis, and a good line drawing of them is provided by Billroth (1858). The earliest description which I have seen is that of Günsburg (1854), but Virchow (1864), in a published set of lectures in which mention is made of these bodies, refers to a previous report by himself in 1850. This last paper has proved inaccessible. Most of these early cases are concerned with their occurrence in lupus and tuberculous adenitis (some of which are clearly sarcoidosis), but more recent publications have noted their presence in pulmonary tuberculosis, leprosy, regional ileitis, and lymphopathia venereum. Pagel (1939), who reported their presence in the vole, referred to the bodies as "spheroid crystals." Many reports have referred to them as "laminated bodies," "peculiar bodies," or simply "inclusion bodies." In the absence of any commonly accepted name for these bodies, and to differentiate them from other named concentric laminated bodies occurring in the tissues, the term "*corpora caepina*" (onion bodies) is suggested as an appropriate descriptive designation.

So far as I am aware, this type of body has not previously been reported in the Fallopian tube. Bozzo (1945), however, recorded the presence of spherical "homogeneous and refrangent" bodies of 4–40 μ diameter in chronic salpingitis. The tissue reaction described was that of chronic non-specific inflammation, and no mention was made of multinucleate giant cells, nor was any illustration provided. In discussing the findings, he favoured the view that the inclusions were analogous to Russell bodies. Of the results of several staining methods, only an affinity for iron haematoxylin suggests an identity with the bodies described above. There is no reference to the use of specific stains for iron and no mention of crystals, anisotropic or otherwise.

It is remarkable that in an extensive search through the literature pertaining to laminated inclusions of the type described only two references have been found to the presence of associated doubly refractile material. Gottstein (1896) described the bodies in tonsillar tuberculosis and noted that they possessed a clear centre and that the "presence of lime salts is confirmed by examination with Nicol prisms." Skavlem and Ritterhoff (1946), referring to inclusion bodies in sarcoidosis, observed that "the colorless and yellowish tinged refractile material often enclosed by a Schaumann body is doubly refractile." These authors, however, do not make the point that such anisotropic material may greatly preponderate over the associated laminated bodies. While the relationship described by Skavlem and Ritterhoff was evident in many sections from the cases here presented, the fact that anisotropic crystalline material was present in some of the sections in which concentric laminated bodies were scanty or absent is a point of some importance. The occurrence of these anisotropic crystals in lesions of a follicular granulomatous type, which include numerous giant cells and may show no caseation, at once raises the possibility that the diagnosis of silicious granuloma might be reached erroneously in cases of tuberculous salpingitis. This is precisely the reverse of the very real pitfall to which Roberts has drawn attention. Moreover, the occurrence of two cases in which non-silicious anisotropic material was found in the Fallopian tube within a period of less than one year, during which time approximately 400 gynaecological specimens

of all types were examined, suggests that the presence of this material is not a rarity. It would therefore seem necessary to examine sections from several levels in the tube, not only, as Roberts suggests, in a doubtful case where the crystals are scanty, but in every case showing anisotropic material in relation to giant cells. The presence of laminated bodies in any part of a lesion presenting doubly refractile material must call for extra care in the interpretation of such crystals, although there is no reason why both non-silicious and silicious anisotropic crystals might not be present in a case of co-existent tuberculosis and silicious granuloma. The method of micro-incineration may provide information regarding the presence or absence of silica, but it is not readily applicable to routine work, and so far as these crystals are concerned the differentiation from silica may be made by treatment of appropriate sections with N/1 mineral acid for half an hour.

Summary

Two cases regarded as tuberculous salpingitis on histological evidence are described. Tuberculous endometritis was found subsequently in one of the cases.

The tubal lesions presented intracellular non-silicious anisotropic crystals and concentric laminated iron-containing bodies.

Comment is made on the unsatisfactory designations of these latter, and the descriptive term "corpora caepina" (onion bodies) is suggested.

The crystalline type of inclusion may greatly predominate or may occur alone, and in sections where caseation is absent the histological lesion closely resembles that of silicious granuloma.

The solubility of the crystals in dilute mineral acids is of differential diagnostic value.

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