SYNOVIAL PATHOLOGIC CHANGES IN SPONTANEOUS CANINE RHEUMATOID-LIKE ARTHRITIS

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The synovial fluid and membrane were studied in 10 dogs meeting the American Rheumatism Association criteria for classic human rheumatoid arthritis (RA). Light microscopic pathologic features were consistent with those found in the human disease. Neutrophilic infiltration of synovium was somewhat more prominent than in chronic human RA, and activated lymphocytes in fluid or membrane were less frequent. The proliferative and plasma cell reaction seemed identical. Electron microscopy (EM) suggested microvascular injury with findings which included electron dense deposits in the vessel walls of 2 dogs. Seven dogs had meshworks of 20-25 nm tubules in tubuloreticular structures (TRS) similar to those seen in human systemic lupus erythematosus and only occasionally in human RA. There were also crystalline arrays of tubules, a configuration previously reported in tumors and virus infections and possibly suggestive of a cellular reaction to virus infection. To date no initiating agent has been identified, but this spontaneous canine disease which is very similar to human RA can provide a valuable model in which to examine pathogenesis of chronic arthritis.

A spontaneous, chronic, erosive polyarthritis similar to human rheumatoid arthritis (RA) occurs in dogs (1-3). This arthritis is of importance to rheumatologists because it may provide the first spontaneously occurring model for the human disease. A preliminary study suggests that canine RA can be responsive to gold salt therapy (4). It is also intriguing that epidemiologic studies (5,6) have shown a greater exposure of human RA patients to dogs and other pets during the 5 years prior to onset of disease than for osteoarthritics and patients with other miscellaneous minor musculoskeletal problems. Examples of coincidental arthritis in pets and owners have been found. Household dogs of patients with systemic lupus erythematosus (7) have also recently been suggested to be clinically and serologically involved. This report describes the gross and the light and electron microscopic (EM) synovial changes in 10 dogs with canine arthritis that fulfilled the American Rheumatism Association (ARA) criteria for classic RA (8).

MATERIALS AND METHODS

All dogs presented to the University of Pennsylvania Veterinary Hospital (UPVH) were screened for symptoms of arthritis. After eliminating from the study dogs with degenerative joint disease, septic arthritis, and polyarthritis associated with systemic lupus, 10 dogs were further studied by x-ray, Rose-Waaler tests for rheumatoid factor, clinical examination, and biopsies to identify those with a definite diagnosis of rheumatoid arthritis.

All dogs diagnosed as having canine rheumatoid-like arthritis met at least 7 of the ARA criteria for a diagnosis of human rheumatoid arthritis (8). Canine RA-like arthritis affected both pure and mixed breeds. The age range at initial presentation was from 13 months to 8 years, and age at onset was from 5 months to 7 years, with 1 male and 9 females affected. Seven dogs had rheumatoid factor titers according to...
SYNOVIAL PATHOLOGIC CHANGES IN CANINE RA

Table 1. Clinical features and synovial fluid finding in rheumatoid-like disease in dogs

| Dog no. | Sex | Arthritis duration, months | Drugs | WBC/mm³ | % PMN | % small lymphs | % activated lymphs | % monocytes | % large macrophages | % SLC | % eosinophils |
|---------|-----|---------------------------|-------|---------|-------|---------------|-------------------|-------------|-------------------|-------|--------------|
| 1       | F   | 18                        | Gold  | 10      | 44    | 0             | 3                 | 0           | 43                |       |              |
| 2       | M   | 6                         | 0      | 6,500   | 15    | 15            | 0                 | 40          | 10                | 10    |              |
| 3       | F   | 18                        | 0      | 2       | 62    | 6             | 0                 | 5           | 0                 | 25    |              |
| 4       | F   | 12                        | ASA    | 54,000  | 94    | 31            | 7                 | 0           | 0                 | 4     |              |
| 5       | F   | 18                        | ASA    | 40      | 31    | 7             | 13                | 6           | 4                 |       |              |
| 6       | FS  | 2                         | 0      | 5,800   | 81    | 7             | 2                 | 4           | 3                 |       |              |
| 7       | F   | 6                         | 0      | 85      | 9     | 0             | 1                 | 1           | 4                 |       |              |
| 8       | FS  | 24                        | ASA    | 38      | 42    | 0             | 10                | 0           | 0                 |       |              |
| 9       | F   | 18                        | ASA    | No fluid studied |   |               |                   |             |                   |       |              |
| 10      | F   | 8                         | 0      | No fluid studied |   |               |                   |             |                   |       |              |

* F = female; M = male; FS = spayed female.
† Dog no. 1 received 12 injections of gold. ASA = aspirin.
‡ WBC = leukocyte count.
§ PMN = polymorphonuclear neutrophils.
¶ SLC = synovial lining cells

Table 2. Light microscopic synovial membrane findings in rheumatoid-like disease in dogs

| Dog no. | Superficial fibrin | Polymorphonuclear neutrophils | Lymphocytes | Plasma cells | Congested vessels | Synovial lining cell proliferation | Hemosiderin in deep macrophages | Edema |
|---------|--------------------|-------------------------------|-------------|--------------|------------------|-------------------------------|-------------------------------|-------|
| 1       | +                  | +                             | +           | +++          | +                | +                             | +                             | +     |
| 2       | +                  | +                             | +           | ++           | +                | +                             | +                             | +     |
| 3       | +                  | +                             | +           | +            | +                | +                             | +                             | +     |
| 4       | +                  | +                             | +           | +            | +                | +                             | +                             | +     |
| 5       | +                  | +                             | +           | +            | +                | +                             | +                             | +     |
| 6       | +                  | +                             | +           | +            | +                | +                             | +                             | +     |
| 7       | +                  | +                             | +           | ++           | +                | +                             | +                             | +     |
| 8       | +                  | +                             | +           | +            | +                | +                             | +                             | +     |
| 9       | ++                 | ++                            | +           | ++           | +                | +                             | +                             | +     |
| 10      | ++                 | ++                            | +           | ++           | +                | +                             | +                             | +     |

* + = occasional; ++ = intermediate; +++ = extreme amount.
Figure 1. Superficial fibrin (F) and hyperplastic lining cells (SLC) in dog no. 3. (Hematoxylin and eosin; magnification × 200.)

Figure 2. Synovial villus from dog no. 8 showing hyperplastic lining cells (SLC) and moderate chronic inflammatory cell infiltration which includes some plasma cells. (Hematoxylin and eosin; magnification × 200.)
vide accurate cell counts or cells for EM examination. All synovial biopsies were obtained before any treatments, other than aspirin, were given the animals. One joint fluid was obtained after initiation of gold salt therapy (Table 1). Synovial fluid cells were classified by Wright's and Sudan stains as described by Traycoff et al (12).

RESULTS

Gross findings. Gross changes included striking synovial proliferation with bony and cartilaginous destruction. All 10 dogs demonstrated proliferative, brown, discolored synovium that in most instances was markedly thickened 1-3 mm. There were large papillae of synovium and long fingers of fibrin present in 4 animals. Mild invasion of synovial tissue into subchondral bone was present in 3 dogs, and massive invading pannus was present in the other 7.

Light microscopy. Table 2 delineates the light microscopy findings. Histologically, synovium demonstrated marked lining cell proliferation in 8 of the dogs examined (Figures 1 and 2). In most instances the underlying connective tissue was equally proliferative with increased numbers of fixed tissue cells. Infiltration of the underlying connective tissue with plasma cells occurred in all 10 dogs (Figure 2). The plasma cells were found to be scattered diffusely in most dogs, although focal aggregations were found as well. More than rare lymphocytes were also found in the synovium of 5 dogs. The lymphocytes were diffusely scattered throughout two of the synovial membranes and were present in more focal aggregates in two. Infiltration with polymorphonuclear neutrophils (PMN) was seen in 5 dogs; in these tissues, the PMN were diffuse in 3 dogs and focal in the other 2.

Deposits of acellular fibrin were easily demonstrated on the synovial surface in 7 dogs (Figure 1). Hemosiderin was recognizable in deep macrophages in 6 dogs. Congested capillaries were seen in 3 tissues and edema in 2.

Electron microscopy. Table 3 shows the EM results. Ultrastructural studies allowed some extension of the light microscopic findings. Finely granular material was frequently mixed in with the prominent surface fibrin. Lining cells could be characterized as including types A (phagocytic), B (synthetic), and C (intermediate) cells (13) with B and C cells (Figure 3) predominating only slightly. Finely granular material and cell debris were phagocytized by some type A lining cells and by prominent deep phagocytic cells. Considerable deep interstitial necrotic debris and fibrin (Figure 4) were found in 3 synovial membranes, as in human RA. The pattern of inflammatory cell infiltration with
predominant plasma cells (Figure 5) was similar to that seen by light microscopy. Note that despite examining multiple blocks by EM, sampling still was limited so that inflammatory cells, for example, were not seen by EM in all dogs. Interstitial polymorphonuclear cells were degenerating (Figure 4) or degranulating in 3 synovia. Plasma cells often had dramatically dilated rough endoplasmic reticulum. Activated lymphocytes with polyribosomes were not identified.

Vessels showed occasional gaps (Figure 6) between endothelial cells and multilaminated basement membranes, but no vessel wall necrosis, fibrinoid, or evidence of virus-like particles was observed. Electron-dense deposits were seen in vessel walls of 2 dogs (Figures 6 and 7), and degranulating polymorphonuclear cells and platelet clumps (Figure 6) were present in vessel lumens of 2 dogs each.

Occasional extravasated erythrocytes and iron in deep macrophages were consistent with the light microscopic finding of hemosiderin deposits in some dogs. Seven synovia had prominent lipid droplets in deep synovial cells or lining cells. No identifiable bacterial or other organisms were found.

Tubuloreticular structures (TRS) as typically seen in human SLE (14–16) were seen in 7 dogs (Figures 3, 8, and 9). These were seen in endoplasmic reticu-
lum (ER) or adjacent to ER in the cytoplasm of lining cells and deep synovial cells with prominent rough ER. Some TRS-containing cells appeared to be plasma cells. Tubules 20–25 nm in diameter were arranged in a loose (or occasionally tightly packed) random meshwork. Tubules of similar 20–25 nm diameter were also seen in crystalline arrays (Figure 10) in 9 dogs including all 7 who had identifiable TRS. Crystalline arrays were documented in cross and longitudinal sections. Some were in the ER, but others were in the cytoplasm or in membrane-bound dense bodies. Acid phosphatase EM histochemistry confirmed the lysosomal nature of these dense bodies with crystalline arrays of tubules in 2 dogs (Figure 11). TRS were never seen associated with acid phosphatase positive areas. Cells with the crystal-like arrangement of tubules in dense bodies also frequently contained other unidentified, highly dense, lipid-like or finely granular material or ferritin granules.

In 3 dogs some round vesicle-like bodies mixed with various types of cell debris were seen in occasional vacuoles or in interstitium (Figure 5). None strongly suggested any specific virus or other organism.

Twenty control dog synovial membranes were reviewed. No TRS were found in 7 normal mongrels used for experimental injection of urates (17), 10 normal mongrels used in study of joint trauma, or 3 osteoarthritic dogs. In two of the supposedly normal mongrels, small crystal-like arrays of membrane bound tubules were found in lining cells.

**Synovial fluid analysis (Table 1).** Total cell counts on the 3 synovial fluids with sufficient volume for leukocyte counts ranged from 5,800 to 54,000/mm³. The widely varying differential counts found are shown in Table 1. PMN predominated in 3 fluids. There were no large mononuclear cells that had phagocytized PMN ("Reiters cells"). LE cells, or other unusual features.

**DISCUSSION**

Since first being reported in the last 10 years (1–3), canine rheumatoid-like arthritis has begun to receive attention as a potential animal model of human disease. Major studies of the disease have been reported from the University of California at Davis (2) and the University of Pennsylvania (1,4,9). Case reports account for an additional 15 cases present in the literature (3,18). All reports agree on the major gross and histopathologic findings. These are described as villous proliferation, hyperplastic synovium, fibrin deposition over the proliferative synovium, bony erosions, and infiltration with mononuclear cells including plasma cells. Pederson (2) did not mention the PMN which were also seen in some
of our dogs, but Scott did (18). Otherwise, our light microscopic findings differ little from previous reports. These findings meet the ARA criteria as characteristic of human RA synovium (8). Necrosis also mentioned in the ARA criteria was not usually appreciated by light microscopy but was seen prominently by EM in 3 dogs. Polymorphonuclear cell infiltration in synovium in our series and in the dog studied by Scott (18) appeared to be slightly more common than in human RA. However, PMN can be seen in some chronic human RA synovial membranes and are even more common in early RA (19). The prominence of hemosiderin deposits was more marked than in most reports of human RA, possibly because dogs abused actively inflamed joints more than humans. Iron was localized, as it is in human RA synovial membranes, predominantly in deep phagocytic cells (20).

We previously reported a single case of only limited EM findings in canine rheumatoid-like arthritis (9); no other report appears in the literature. The absence of activated lymphoblasts in our synovial biopsies appears to be different from human RA (21), but this may represent in part a sampling problem since activated lymphocytes were seen in some synovial fluids.

Microvascular changes have not been as prominent in human RA of chronic duration as in these dogs, but these changes have been emphasized in early human RA of up to 6 weeks duration (19,22). The presence of large electron-dense deposits in vessel walls of 2 dogs resembled findings in some early human RA (19) which suggests the possibility of deposition of immune complexes in these vessels. These dense deposits in the dogs have not yet been further characterized. Platelet plugging, degranulating intraluminal cells, gaps between endothelial cells, and multilaminated vascular basement membranes were also evidences of some microvascular injury.

The tubuloreticular structures found in synovial membranes in 7 of our rheumatoid dogs are familiar to rheumatologists because of their frequent occurrence in human systemic lupus erythematosus (14–16). They have also occasionally been described in human RA (14,23). To our knowledge, EM studies to search for TRS in synovial membrane or other tissues in canine SLE have not been performed. Tubuloreticular structures have also been identified in various other tissues (in addition to synovium) of patients with systemic lupus erythematosus (14–16), in muscle tissue of patients with dermatomyositis (14,29,30), and in a variety of sites in other diseases. They have been found in infectious mononucleosis (31), human lymphoma cell lines growing herpes simplex (32), human herpes encephalitis cerebral tissue (33), dog intestine in coronavirus infection (34), and a variety of tumors (35). Thus there seems to be a suggestion of association of TRS with rheumatic disease, virus infection, and neoplasm. The nature and cause of TRS are not known. Tubuloreticular structures differ from paramyxoviruses, including canine distemper virus, by the regular association of TRS with the endoplasmic reticulum and the smaller (15–17 nm) diameter fibrillar nucleocapsids of the virus (24,25). Although nucleic acid is apparently not demonstrable in TRS (36), Pincus et al (37) have suggested that they might be a cellular reaction to virus infection.

The crystalline arrays of tubules seen in 9 rheumatoid-like dogs have not been reported in human RA. These inclusions appear virtually identical to clumps of cytoplasmic tubular arrays without binding membranes found in the cytoplasm of endothelial cells in placentas.
Figure 7. Electron-dense, finely granular deposits (G) between venular endothelium (E) and pericyte (P) in synovium of dog no. 8. (Electron micrograph, magnification x 34,000.)

from patients with SLE; such inclusions are not found in normal placentas (26). Those in the human material were believed to be protein of unknown type and could be distinguished morphologically from the membrane-bound Weibel-Palade bodies (27) which earlier had been confused with viruses (28). The significance of the crystalline arrays, as with the TRS, is unknown, but they have also been suggested to possibly be a result of virus-cell interaction because of the other diseases in which they are seen. Crystalline arrays have been reported in ER and dense bodies of dogs with meningeal tumors induced by Rous sarcoma virus; they are not found in normal dog meninges (38). Similar arrays have also been seen in a wide variety of other virus infections including monkey kidney cell cultures infected with rubella virus (39), rabbit experimental herpes encephalitis (40), and Aleutian disease of mink (41). Schaff et al (42) have found crystalline arrays of similar tubules with light cores that are an estimated 25 nm (22–28 nm) in diameter in ER of rabbit myxosarcomas. There were also identical size tubules in ER arranged more like the typical tubuloreticular structures in the same tumors. Schaff (36) and others (43) have suggested that there may be a relationship between the two types of tubules. Some relationship is also supported by our studies showing the 2 kinds of structures together in 7 of the RA dogs and some densely packed, but not crystalline, TRS (Figure 8) that might suggest a transition phase between these and crystalline arrays seen in rough endoplasmic reticulum.

No type C particles or coronavirus-like particles have been found in our dogs. They have occasionally been noted in human rheumatoid synovial membrane only with very early disease (19) or with cocultivation (44). The wide variety of types of debris in the dog synovium as well as human RA could certainly harbor material from an infectious agent that is no longer morphologically identifiable.

There have been a few light microscopic studies of dog synovial membrane in other states that should be compared with our rheumatoid-like dog findings. Dog synovial membrane in culture-positive chlamydia arthritis has been described by Young et al (45) as showing large amounts of superficial fibrin, hyperplastic lining cells, and infiltration of neutrophils and plasma cells. A group of culture-negative dogs (46) with non-
ings reported included increased numbers of intermediate type (13) synovial lining cells, some of which included large vacuoles containing particles of various sizes and electron density. They did not report TRS or crystalline arrays or evidence of infectious agents. As noted above, we have observed occasional crystalline arrays but not TRS in apparently normal dog synovium.

The synovial fluid findings in our dogs with RA-like disease are quite consistent with the generally accepted findings in human RA (49). Polymorphonuclear neutrophils or mononuclear cells predominated in different fluids. Prominence of activated lymphocytes, which we recently reported in human RA effusions (12), was seen in only 2 dogs.

We recognize that dogs with systemic lupus erythematosus can also have polyarthritis (50,51). Systemic lupus was excluded in our dogs by absence of any of the characteristic clinical or laboratory findings. We are not aware of EM studies on lupus synovium in dogs. A light microscopy study (50) on synovium of a dog with fea-

Figure 8. Tubuloreticular structures packed densely in cisterns of rough endoplasmic reticulum (arrows) in deep synovial cell of dog no. 3. (Electron micrograph, magnification × 31,000.)

erosive arthritis, including some with SLE and some undiagnosed, were reported to show superficial fibrin, a paucity of synovial lining cells, and predominantly neutrophilic infiltration with mononuclear cells. There was no villous hyperplasia or pannus. Dogs whose knees were experimentally injected with cartilage homogenate (47) developed synovial round cell infiltration after several months. As with human disease, most synovial membrane findings are not diagnostic. RA findings can be mimicked by other diseases, but synovial findings in conjunction with other features can be helpful in diagnosis (8).

Previous electron microscopic studies on dog synovium in other diseases include those of Huxtable and Davis (48) who studied synovia of 17 young greyhounds with erosive inflammatory polyarthritis and negative tests for rheumatoid factor. Electron microscopic find-

Figure 9. Loosely packed tubuloreticular structures at the rough endoplasmic reticulum of dog no. 6. (Electron micrograph, magnification × 38,000.)
Figure 10. A, Crystalline arrays of 20-24 nm tubules in cross section (arrow) were closely associated with the rough endoplasmic reticulum in dog no. 10. (Electron micrograph, magnification x 40,000.) B, Crystalline arrays, as described in A, found in dense bodies in dog no. 3. (Electron micrograph, magnification x 31,000.)
Figure 11. Acid phosphatase histochemistry clearly identifies some light crystalline longitudinally cut parallel tubular arrays lying with the dark enzyme in lysosomes. N = nucleus. (Electron micrograph, magnification × 36,000.)

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