Villonodular synovitis in the dog

A report of four cases

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Summary
Four cases of villonodular synovitis were diagnosed by histopathology. All four dogs were treated medically with either carprofen or a combination of carprofen and glucosamine complex (Cosequin®). In three of the dogs the condition improved significantly, and these dogs returned to normal workload.

Keywords
Villonodular synovitis, arthroscopy, medical treatment, shoulder joint, stifle joint, dog

Introduction
Villonodular synovitis (VS) is an infrequently diagnosed cause for lameness in dogs. Four cases have been reported previously, all of which occurred in medium or large breed dogs. Hip and stifle joints were affected. Treatment consisted of synovectomy in conjunction with corticosteroids. The outcome was unfavourable in most cases.

The aim of this paper is to present four cases of canine VS, including arthroscopic findings in three of the cases, and to summarise facts about the disease as reported in humans and animals. Two of the cases occurred in small breed dogs (Dachshunds). In three of the dogs, the shoulder joint was affected. All dogs were treated medically, without synovectomy. Two of the dogs returned to full function.

The use of arthroscopy for routine examination of intra-articular lesions may reveal that VS is a more common condition than has been previously observed.

Literature review
In humans VS is an uncommon condition affecting the synovial membrane of joints, bursae and tendon sheaths (16, 19, 23, 30, 33, 35). It is usually a disease of young adults or middle-aged persons. The disease tends to be progressive, causing mild or intermittent pain, swelling, episodes of locking, and bloody effusions to the joint (3, 6, 12, 16, 19, 23, 32, 33, 35, 37, 42). Two forms have been described in humans, one being local and the other diffuse. The local or circumscribed form is more common. It occurs as a pedunculated or sessile growth from the synovial membrane. The diffuse form affects the entire synovial lining and appears as a pigmented thickened membrane with nodular or villous masses (19, 30, 32, 42). In the horse VS has been reported in the metacarpophalangeal and metatarsophalangeal joints (22, 34). The disease appears to be somewhat different from the condition described in humans (3, 25). One case of VS has been reported in the hock joint of a goat (13).

Histologically, VS is characterized by hyperplasia and thickening of the synovial lining and stromal cells. The proliferative synoviocytes may spread into the fibrous layers of the joint capsule, but they do not invade adjacent soft tissues (32). Most of the surfaces are altered by complex villous formation or areas of nodular surface formed by fused villi. Deeper areas are either of a solid pattern or contain irregular slits lined by synovial cells. There is fibrous tissue intermixed with a polymorphic population of synovial cells, foam cells and hemosiderin laden histiocytes. There are also cells containing variable amounts of iron or lipids. Small numbers of macrophages, some of which may be filled with hemosiderin, and small lymphocyes are scattered diffusely in the lesions. Mitotic figures may occasionally be demonstrated as well as numerous multinucleated benign giant cells. Binucleated synoviocytes are not uncommon (1, 7, 13, 16, 20, 30, 33, 42). In one study the multinucleated cells are believed to be osteoclast-like (11). In VS in humans, studies of the cell populations show that the number of synoviocytes being double positive for both macrophage and fibroblast markers are significantly higher in the diffuse form compared to the localized form.
In the accompanying inflammation cytotoxic cells predominates. This suggests that the proliferating macrophage-like synovial cells and the cytotoxic lymphocytes could contribute to pathologic changes of both diffuse and localized VS in humans (3). The giant cells and synovial cells also often show diffuse and intense immunoreactivity for cytokines and metalloproteinases (MMPs). The macrophages show a less intense and diffuse staining for cytokines but moderate for MMPs, whilst the staining of fibroblasts for cytokines is reported to be minimal (31, 40). Electron microscopy reveals swollen endothelial cells and multiple layers of basal membrane around small synovial vessels. The cytoplasm of many of the synovial cells and macrophages contain fine diffuse electron-dense particles, presumably rich in iron (4).

Villonodular synovitis is rarely diagnosed in the dog. Previous reports on four cases of VS have been published (18, 23, 25, 39) (Table 1). The condition may occur in any major weight-bearing joint, and is more likely to affect older dogs of both genders and of medium and large breeds (32). Affected dogs showed a gradual onset of lameness or joint distension. The affected joint was initially warm or painful. Later pain due to joint instability may be evident if erosions of the bone occur along the joint margins (18, 25, 32, 39). All of the dogs had a history of progressive lameness without evident trauma. Radiography revealed mild to moderate soft tissue swelling and narrowing of the joint space, mild periosteal new bone formation and, in several cases, subchondral osteolytic lesions (18, 23, 35). Synovial fluid from affected joints was discoloured, red or brownish, and considered to be of the inflammatory or degenerative type with no growth of bacteria on cultivation (18, 23, 25, 39). At arthrotomy the synovial membrane had a yellowish or brown pigmentation, and showed diffuse nodular proliferation and thickening (23, 25, 39).

Material and methods

Medical records of four cases of VS diagnosed at Strömsholm Referral Animal Hospital between February 2001 and January 2004 were reviewed.

Case reports

Case 1

A seven-year-old male Dachshund was presented with a history of four months of lameness of the left front leg. The lameness was progressive and in the last four weeks the dog had become non-weight bearing on the leg. The dog showed marked discomfort on palpation and extension of the shoulder joint. The joint was distended and the proximal humerus had a diffuse contour on palpation. The musculature of the affected leg was slightly atrophic. Despite sedation the dog was markedly painful on manipulation of the shoulder joint.

Radiographically, there was moderate osteophyte formation on the caudal edge of the humeral head and minor osteophytes on the caudal edge of the glenoid. The subchondral bone had a different structure than normal in the left proximal humerus.

Synovial fluid from the joint was macroscopically normal. Analysis revealed a cell count of 1450 cells/mm³, 85% of which were large mononuclear cells and 15% small mononuclear cells. No bacteria were seen. Serological tests for Borrelia and Anaplasma were negative.

Arthroscopy of the shoulder joint revealed severe generalised synovitis with markedly hypertrophic folds of synovial membrane of the entire cranial part of the joint. The biceps tendon and its sheath were normal. Medially and posteriorly in the synovial membrane several haemorrhagic nodules were noted. The cartilage of both joint surfaces was severely eroded, with eburnation on the main weight bearing surfaces. Several biopsies were taken arthroscopically from the synovium. The joint was vigorously flushed.

Histopathological examination showed villonodular hyperplastic synovitis. The synovial membrane formed hyperplastic proliferations with infiltrates of mixed inflammatory cells. Beneath this layer focal fibroplasia was seen. Bacteria were not seen. The histopathological diagnosis was hyperplastic villonodular synovitis.

Treatment was started with carprofen (Rimadyl vet®, Orion Pharma AB, Sollentuna, Sweden), 2.0 mg/kg twice daily. At follow-up two weeks postoperatively the lameness had improved, but the dog was stiff after rest and occasionally lame. There was no pain on palpation of the shoulder. The synovial fluid was normal macroscopically. The shoulder joint was injected with 1 ml of triamcinolonhexacetone (Lederspan®, Meda AB, Solna, Sweden).

At follow-up one month post injection, lameness had again increased. Treatment with carprofen in the same dose continued. Another month later the dog had improved again, with no lameness after rest or exercise. At follow-up by telephone, the condition improved further according to the owner, and the dog became free from lameness as long as the medical treatment con-

Table 1  Previously reported cases of VS.

<table>
<thead>
<tr>
<th>Breed</th>
<th>Sex</th>
<th>Age</th>
<th>Affected joint(s)</th>
<th>Tx</th>
<th>Results</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross breed</td>
<td>Female</td>
<td>10 y</td>
<td>Stifles bilateral</td>
<td>Synovectomy and Prednisone-1 mg/kg for 4 weeks, tapering down for 2 weeks</td>
<td>5 and 18 mo. Gradual deterioration after cessation of steroids</td>
<td>25</td>
</tr>
<tr>
<td>German Shepherd</td>
<td>Male</td>
<td>8 y</td>
<td>Radiocapal</td>
<td>Not reported</td>
<td>Not reported</td>
<td>18</td>
</tr>
<tr>
<td>Labrador</td>
<td>Male</td>
<td>8 y</td>
<td>Coxofemoral</td>
<td>Femoral head and neck resection</td>
<td>Doing well until VS developed in contralateral coxofemoral joint</td>
<td>23</td>
</tr>
<tr>
<td>Labrador</td>
<td>Female</td>
<td>4 y</td>
<td>Stifle</td>
<td>Synovectomy</td>
<td>Doing well, euthanized for unrelated reason after 9 months</td>
<td>39</td>
</tr>
</tbody>
</table>
Canine villonodular synovitis continued. The dog was euthanatized one year post-operatively because of disc herniation.

**Case 2**

A nine-year-old male Dachshund was referred because of lameness of the left front leg for over six months. The degree of lameness varied between mild and severe. Serological testing for Borrelia and Anaplasma had been negative. Treatment with NSAID, corticosteroids and an intra-articular injection of hyaluronic acid had given only temporary relief.

Clinical examination showed severe lameness of the left front leg. Palpation of the left shoulder joint and the biceps tendon was painful. Range of motion of the joint was normal, but maximal flexion and extension elicited pain. There was no instability.

Standard radiographs of the shoulder joint showed moderate osteophytes at the caudal edge of the humeral articular surface and mild mineralization of the biceps tendon sheath (Fig. 1). The synovial fluid was bloodstained and contained 80% neutrophilic granulocytes, 13% macrophages and 5% lymphocytes. The cell population was not considered to be caused by infection, since it was the same as the population in the systemic circulation and contained a relatively high proportion of macrophages. Therefore, bacterial culture was not done.

At arthroscopy the synovium of the left shoulder joint had an intense yellow-orange colour with a rough surface where several prominent tissue masses protruded from the synovium, especially in the caudal part of the joint (Fig. 2). Several samples were taken for cytological and histopathological examination with an arthroscopic biopsy forceps. Cytological examination showed mature lipocytes, erythrocytes and muscle cells, together with a few large mononuclear cells resembling synovial membrane cells, with more of a reactive than neoplastic appearance (Fig. 3). Histopathological examination revealed marked infiltrates of mononuclear cells with cosinophilic cytoplasm, large rounded nuclei and an increased mitotic activity in a marked proliferative synovial membrane. Macrophages containing hemosiderin were also present (Fig. 4). There was no bacteria. The histopathological diagnosis was pigmented villonodular synovitis.

Treatment was started with carprofen, 2.0 mg/kg twice daily. At follow-up by telephone, the owner reported that the dog did not seem to be in pain, but the lameness had not improved and the dog continued to show stiffness of the shoulder joint. The lameness slowly progressed, and led to euthanasia two months after arthroscopic examination.

**Case 3**

A nine-year-old female golden retriever was referred with a three-month history of intermittent left hind leg lameness of acute onset. The lameness had progressed lately. At clinical examination the left hind limb was non-weight bearing. Severe muscle atrophy of the limb was noted. The stifle joint was distended and had a decreased range of motion, but was stable on manipulation. A firm painful swelling could be palpated in the area of the lateral fabella. Standard radiographs of the stifle joint showed prominent osteophytes around the lateral fabella. Moderate osteophytes were noted on the patella and laterally on the proximal tibia.

Arthrotomy of the left stifle joint was performed. The joint capsule was markedly fibrotic and thickened. Cruciate ligaments and menisci were normal. Several biopsies were taken from the joint capsule and synovium.
On histopathological examination the joint capsule and synovium consisted of fibrotic tissue with focal areas of synovial cells and some pigmentation of macrophages. Signs of mucine deposits were found in the fibrous tissue. No bacteria were seen. The histopathological diagnosis was pigmented villonodular synovitis and chronic indurative synovitis.

Treatment was started with carprofen, 1.75 mg/kg twice daily, and physiotherapy in the form of daily massage and stretching of the joint in conjunction with frequent short walks on a leash at slow tempo. An intra-articular injection with 1 ml of triamcinolonehexacetonide was given one month postoperatively. At follow-up by telephone, the owner reported that the dog was sound and had returned to full work load hunting. She was euthanatized one year postoperatively for unrelated causes.

Case 4

A six-year-old female Flat Coated Retriever was referred because of a lameness of the right front leg of five months duration. Treatment with carprofen had improved the condition. At clinical presentation the dog had moderate lameness and abduction of the right front leg. The shoulder joint was mildly distended and painful on palpation. Range of motion of the shoulder joint was moderately decreased, and manipulation of the joint elicited severe pain.

Radiographs in mediolateral and mediolateral oblique projection showed signs of diffuse degenerative joint disease of the shoulder joint with mild osteophytes at the insertion of the biceps tendon and caudal part of the humeral head. No changes in the subchondral bone were noted. The synovial fluid was pale orange in colour and turbid. Microscopic analysis revealed a cell count of 51 000 cells/mm³, consisting of 89% neutrophilic granulocytes, 7% large and 4% small mononucleated cells. The protein content was 43 g/L. Bacteria were not seen on cytological analysis. Microbiological analysis was not performed.

On arthroscopic examination the biceps tendon sheath was normal, but moderate synovitis was noted around the insertion of
the tendon. The joint cartilage was normal. Medially in the synovium signs of acute and as well as more chronic synovitis were noted. There was a minor tear in the medial gleno-humeral ligament. Medial to the ligament was an area with proliferative yellowish tissue, from which several biopsies were taken.

Histopathological examination showed severe synovitis with round nodules and villi formation. The inflammation consisted of foamy macrophages with lipid-looking vacuoles. A moderate number of neutrophilic granulocytes were found, together with lymphocytes and plasma cells. The villi were lined with thickened hypertrophic synovial cells and contained neutrophilic granulocytes and foam cells (Fig. 5). No bacteria were seen. A diagnosis of chronic pyogranulomatous and villonodular synovitis was made.

Treatment with carprofen, 1.77 mg/kg twice daily, and cefalexin was started. No improvement was noted. Two weeks later, when adding a complex of glucosamine, sodium chondroitin sulphate, glucosaminoglycans and manganese (Cosequin DS\textsuperscript{®}, Nutramax Laboratories Inc., Edgewood, Maryland, USA) two capsules morning and one evening, the lameness resolved almost completely for six weeks. When the latter treatment was discontinued for three weeks lameness recurred, as reported by the owner at follow-up by telephone.

**Discussion**

As in previously published papers, all of the cases in the present report were middle-aged to older dogs (18, 23, 25, 29). Earlier reports were on dogs of medium to large breeds, and to the best of the author’s knowledge the condition has not been previously reported in a breed as small as a Dachshund.

The diagnosis of VS may be suspected by history and clinical, radiographic, arthroscopic and synovial fluid examinations, but must be confirmed by histopathological examination. Clinical findings are unspecific changes indicating joint disease. There are no biochemical markers of VS to be used in synovial fluid analysis. Diagnostic imaging techniques, such as standard radiography, ultrasound or magnetic resonance imaging, can identify lesions of unspecific joint disease and, in some cases, changes in the subchondral bone, but can only suggest the diagnosis of VS (6, 41). Magnetic resonance imaging may be more diagnostic in characterising the lesion if it contains hemosiderin deposits (5, 26). Scintigraphy can sometimes be useful in conjunction with other diagnostic imaging modalities (24) to diagnose an inflammatory reaction. Arthroscopic findings are unspecific, suggesting active synovitis.

The anamnestic signs and clinical findings in all four of the present cases were similar to those previously reported. All dogs presented with a severe chronic lameness. In two dogs the lameness was non-weight bearing. The lameness had in three cases either varied in severity or been intermittent. In two cases the lameness was progressive. All affected joints were painful on palpation and/or manipulation. In three out of four dogs the joint was distended. These unspecific findings are in consistency with earlier reports, where distension of the joint on palpation was reported in all cases except with hip joint involvement. Pain on manipulation of the affected joint was noted in three of the four previous reports (18, 23, 25, 39).

Radiographic appearance in previously reported cases was distension of the joint and soft tissue swelling. Subchondral osteolytic lesions with or without mild adjacent sclerosis may occur, as well as mild periosteal new bone formation (18, 23, 25, 32, 39). Mild to moderate radiographic changes were seen in the shoulder joints of cases number 1 and 2 in this report. The radiographic changes were more subtle in Case number 4, but located in the same areas. Radiography of the stifle joint of Case number 3 showed moderate osteophyte formation around the affected joint.

In three of the dogs reported in this paper, synovial fluid was analyzed. All three samples showed an orange or reddish discoloration. Two of the samples showed increased cellularity. The same has been noted in two of the four earlier reports (23, 39). Microbiological analysis was not made in the present cases.

Arthroscopic appearance of VS in dogs has not been described before. All three joints that were examined arthroscopically had prominent pathologic findings. All of the three dogs had a severe general inflammation and hypertrophy of the synovial membrane. In two cases the synovium had a yellowish discolouration. The joint surfaces were normal. In the third case small haemorrhages in the joint capsule were noted and the joint cartilage was severely eroded. The biceps tendon sheath was normal in all three cases, but in one case there was a moderate synovitis around the origin of the tendon. In the fourth case, in which arthrotomy was made, the joint capsule of the stifle joint was markedly fibrotic and thickened. In earlier published reports, similar changes have been noted, with a moderately to severely proliferated and thickened synovial membrane and/or joint capsule with yellow or brownish discoloration (23, 25, 39). Of the cases presented in this report, three were of the diffuse type of VS with involvement of a large part of the joint capsule, while one was more localized (case no 4). In previous reports, lesions were more diffuse (23, 25, 39).

Three of the earlier published papers on VS in dogs reported villous hypertrophy of synoviocytes together with hemosiderin deposits and polymorphonuclear and plasma cells in the subsynovium (23, 25, 39). Histopathologic findings from the synovium of the dogs in this paper were similar, with hyperplastic proliferation and infiltrates of a mixture of inflammatory cells – hemosiderin-containing macrophages and mononuclear cells resembling synovial cells -, synovial hypertrophy and focal fibroplasia. This is also in accordance with a recent study of cell populations in human VS (3).

The aetiology and pathogenesis of VS is still unclear. Neoplasia, immunologic disorders, disturbed lipid metabolism, visceral Leishmaniasis, trauma, haemophiliac arthropathy and intra-articular haemorrhage have been suggested as possible causes in humans (1, 4, 7, 13, 28, 29, 32, 33). In horses it has been hypothesized that poor conformation in conjunction with repetitive trauma may cause the disorder (35). Lesions similar to VS have been induced experimentally in dogs and rabbits after intra-articular injection of autogenous blood or sterile physiological saline solution (19, 20, 42).

In humans, horses and dogs, partial or total synovectomy has been reported in the treatment of VS (4, 9, 14, 15, 23, 25, 33, 35, 39).
Synovectomy and adjunctive radiation therapy or intra-articular deposition of radioisotopes have been reported in humans (6). Arthroplasty is recommended in patients where the condition is disabling. Recurrence is common (1, 7, 8, 12, 13, 21, 34, 37, 41). Radiation has also been used in horses (2, 29). Synovectomy has been reported in conjunction with cryosurgery as treatment for the diffuse form in humans (27). Treatment with anti-tumour necrosis factor 

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References