NORGES VETERINÆRHØGSKOLE

PUBLIKASJONER 1997

NORWEGIAN COLLEGE OF
VETERINARY MEDICINE

PUBLICATIONS 1997

OSLO 1998

NORGES VETERINÆRHØGSKOLE

PUBLIKASJONER 1997

NORWEGIAN COLLEGE OF
VETERINARY MEDICINE

PUBLICATIONS 1997

OSLO 1998

INNHOLD. *CONTENTS*

Dominantly inherited renal cystadenocarcinomas, nodular dermatofibrosis and uterine leiomyomas in German shepherd dogs

Lars Moe

Department of Small Animal Clinical Sciences, Norwegian College of Veterinary Medicine, P.O.Box 8146 Dep., N-0033 Oslo, Norway.

Abstract

The clinical and pathological features and inheritance of the syndrome of renal cystadenocarcinomas, nodular dermatofibrosis and uterine leiomyomas in German shepherd dogs are reviewed. The syndrome usually presents as numerous small, firm subcutaneous nodules, first detectable in the legs and head between six and seven years of age. Multiple renal cysts and cystic adenocarcinomas that may metastasize, are diagnosed between seven and nine years, while the multiple uterine tumours are rarely found clinically. Histopathologically there is evidence for multiple primary neoplasms in three different locations with metastasis occurring only from the renal tumours. The presence of the skin nodules is a marker for the renal cysts and cystadenocarcinomas, and for uterine leiomyoma in the bitch. The syndrome is inherited in an autosomal dominant manner. The specific gene(s) involved is unknown, but different possibilities are discussed. Comparative aspects of the syndrome are mentioned and the possible role as a model for similar human hereditary diseases is discussed. The genetic and pathogenetic mechanisms of the syndrome are the subject of future research.

Introduction

A neoplastic syndrome characterized by multifocal renal cystadenocarcinomas and nodular dermatofibrosis, and, in the bitch, by uterine leiomyomas has been described from Norway (1, 2, 3, 4, 5), and several other countries (6, 7, 8, 9, 10, 11, 12, 13, 14). All these dogs had multiple cysts in the kidneys and renal adenomas or cystadenocarcinomas. Although some articles have focused on the nodular dermatofibrosis and not always reported renal cysts and tumours (12, 15, 16, 17), it has not been shown that these dogs had normal kidneys. Therefore, until otherwise demonstrated, the nodular dermatofibrosis is always expected to occur simultaneously with renal cysts and cystadenocarcinomas, and not as a solitary entity.

Multiple renal cysts were first described in Norway in a German shepherd dog by Lium and Svenkerud in 1967 (18). However, no skin nodules were reported from this case. In retrospect, it is not unlikely that these lesions may have been

5

overlooked, as this was also the case for other dogs during the initial years (1979-1980) of the study of the disease (4, 5). The striking feature both clinically and pathologically was the enlarged neoplastic kidneys and less attention was paid to any dermatological findings. Since the early 80´s nodular dermatofibrosis has been an easily detectable hallmark of the syndrome, and I have not diagnosed a single dog with nodular dermatofibrosis as a solitary entity without concomitant renal disease.

The present article reviews the clinical signs, pathological findings, and discusses the aetiology and some comparative aspects of the condition.

Breed and occurrence

The syndrome of renal cystadenocarcinomas, nodular dermatofibrosis and uterine leiomyomas is a rare disease first reported to occur in German shepherd dogs (1, 2, 3, 15). In 1991, the first non-German shepherd dog with the syndrome was described, as a German shepherd mixed-breed dog (16), and the syndrome has also been diagnosed in a Golden retriever (19). In Norway, the condition was not diagnosed in other breeds until 1997. Two mixed-breed male dogs were diagnosed to have bilateral, multiple very small renal cysts at approximately one year of age (Moe L and coworkers: submitted for publication). These male dogs where the progeny of a purebred German shepherd dog bitch that suffered from the syndrome. The findings indicate that the syndrome may occur in breeds other than purebred German shepherd dog.

Primary renal tumours account for only 0.3 to 1% of all neoplasms in the dog (20, 21, 22), while data from the Norwegian Cancer Registry of Dogs showed that 6% of all German shepherd dogs with tumours (n=423) had kidney tumours (22). Only two cases of neoplasms in the kidney of a total of 336 tumours were recorded in a survey of necropsy specimens from 2,500 German Shepherd dogs (23). In one study 79% of 57 primary renal neoplasms diagnosed, were found in this breed, while German Shepherd dogs only constituted 13% of the total number of dogs (N=9068) necropsied (4). The renal cystadenocarcinomas forming a part of the present syndrome are the dominant renal tumour in German Shepherd dogs in Norway and constituted more than 90% of the renal tumours diagnosed since 1967 at the Norwegian College of Veterinary Medicine (Moe L and coworkers: unpublished results).

The syndrome affects both sexes equally. The male:female (M:F) ratio was 1.1, while the corresponding M:F ratio of the reference population of German shepherd dogs was 1.25 at the same clinic during the same period (5). A male predominance has been reported in other renal tumours of both man (M:F ratio 2 to 3) (24, 25, 26), and dogs (M:F ratio 1.6 to 2.1) (20, 27).

Inheritance

The neoplastic syndrome was, during a 20 years period of study in Norway, only diagnosed in the German shepherd dog breed (3, 5). The majority of proband dogs belonged to a few families of dogs and the affected dogs could be traced back to a low number of ancestors (3, 4). Pedigrees of affected dogs from Sweden, Denmark and Germany showed the same ancestry (Moe L and Lium B: unpublished results). It has been proposed that renal cystadenocarcinomas and nodular dermatofibrosis is inherited through an autosomal dominant trait of inheritance (4). A recent publication from Australia reported a familial occurrence of nodular dermatofibrosis and renal cystadenoma in related German shepherd dogs (12).

A thorough examination of pedigrees of 95 affected Norwegian dogs confirmed the earlier suggestion that the syndrome is inherited in an autosomal dominant way (28). The health status of parents and littermates of proband dogs was often unknown. However, in all cases where the health status of parents was known, only one of the parents had the syndrome. Affected offspring were diagnosed following either an affected mother or father. Several affected bitches that were mated with different males produced affected offspring in all litters. In some pedigrees, the condition occurred in each generation, and in one family, the neoplastic syndrome was verified in five successive generations. The proportion of affected dogs in a litter was approximately 50% of the dogs at risk. Autosomal dominant inheritance can usually be detected if the trait occurs in each generation, as it did in many of the pedigrees. Since the sex ratio of affected dogs was close to one, an X-linked inheritance can be excluded.

The hypothesis of an autosomal dominant mode of inheritance was tested by reproduction of the syndrome through a test mating in 1985 (29). An affected purebred male dog was selected and mated with a purebred, unrelated, unaffected female. The seven offspring were euthanized due to diseases at 8 years of age or older. Five offspring, i.e. 71%, were affected while two were unaffected. The hypothesis was strongly supported by this test mating.

Pathogenesis - Multiple primary neoplasms

Several questions concerning the pathogenesis of the syndrome have been raised. What is the nature and relation between the different lesions in the kidneys, skin and uterus? Which organ develops pathological changes first?

Clinically, the mean age at the first detection of skin nodules is 6.4 years, but renal cysts and nodules in the skin have been detected at four to five years of age (5, 29). There is no evidence to support a theory of metastatic spread of the disease for instance from the kidney to the skin or uterus. The cell morphology of the neoplastic tissue in each organ is quite different.

Based on the present level of understanding, the hypothesis has been advanced that the skin nodules, the renal cystic tumours and the uterine tumours develop independently. Thus, the syndrome represents an example of multiple primary neoplasms (30).

Recently, it has been found that two mixed-breed male dogs had bilateral, multiple, very small renal cysts at one year of age (Moe L and coworkers: submitted for publication). The cysts seemed to be typical rounded structures outlined by a continuous epithelial layer of tubular origin. Since these dogs were offspring of a bitch that suffered from the syndrome, it is probable that they will also develop the syndrome later in life. These findings indicate that renal changes may be detected at a very early age, before any skin nodules may be present, and that the formation of renal cysts may be a principal event in the later development of renal carcinomas, as occurs in humans with polycystic kidney disease (31, 32). There is a high incidence of small adenomas and many cases of adenocarcinomas in human patients with autosomal dominant polycystic kidney disease.

There also seems to be a tendency towards malignant transformation of the renal lesions with advancing age in dogs predisposed to renal cystadenocarcinomas (4, 5, 8, 10 12,19). One mechanism for the development of the renal cystadenocarcinomas may be a progressive transition from epithelial cell hyperplasia to adenomas and adenocarcinomas (4). A mechanism for the cyst formation may be a proliferation of epithelial cells causing local obstruction and mechanical blockage of renal tubuli with subsequent cystic dilatation of proximal segments (4). This hypothesis has been replaced by another theory based on recent research from humans and laboratory animals that concludes that renal cysts derive from microscopic renal tubules that enlarge progressively to form a diverticulum or saccular expansion of the tubule wall (31). The accumulation of fluid within the cyst cavity is derived from glomerular filtrate or transepithelial fluid secretion. The cyst may then become disconnected from the tubular structure.

Sporadic renal cell tumours in man arise from proximal tubules and a similar origin is suggested for sporadic canine neoplasms. Renal cystadenocarcinomas in German shepherd dogs, would also appear to have a tubular origin. Which genes are involved? Since the syndrome is inherited, several types of candidate genes may be involved such as tumour suppressor genes, or oncogenes, or several closely associated defect genes may be responsible.

Is there an influence of environmental factors? The syndrome appears in middle-aged to old German shepherd dogs and the inherited genetic disposition needs

time to develop a tumour. External factors such as irradiation or chemicals, or endogenous factors such as hormones may play a role in the process of cancer development. The variation in the extent of renal lesions, and the number of nodular dermatofibrosis and the variation in the age of the first appearance of signs, could be explained by modifying external and other factors. Such factors could probably be common environmental component(s) which usually, in normal individuals, do not cause tumours. So far, knowledge of these factors is limited.

Clinical signs

Multiple tumours or nodules in the skin (Fig 1), and other skin diseases, are the main presenting complaint of the syndrome (5), although a whole range of signs may be detected by the owner, such as distention of the abdomen, gross haematuria, polydipsia and depressed general condition.

The clinical signs vary considerably between dogs, depending on the age of the dog and the stage of the disease at which the dog is examined. Generally, in most dogs with increasing age, the bilateral renal changes are more pronounced, the number of skin tumours increases, and the uterine tumours increase in size (3, 5, 29). Until four years of age no clinical signs are seen. When the clinical diagnosis was both multiple irregular renal masses and multiple nodular dermatofibrosis, the mean age at diagnosis was 8.2 years (5).

The general condition of affected dogs varies with the stage of the disease (5). Many dogs have a normal general condition at the time of diagnosis, but develop a depressed general condition later in life. Apart from the multiple skin nodules, non-specific signs such as weight loss, abdominal distention, and respiratory distress are commonly found. Abdominal pain and respiratory dyspnoea may be seen as a result of peritonitis caused by the rupture of renal cysts and / or metastasis of the renal tumours. Abdominal pain and haematuria, which are two of the common presenting symptoms of humans with renal carcinoma (24), only occurred in 25% or less of the dogs with renal cystadenocarcinomas (5). Gross haematuria and polydipsia may also develop in some dogs after the initial diagnosis has been established. Gross haematuria was usually an intermittent feature, lasting for a few days up to weeks.

Enlarged or distorted renal masses may be palpated in the kidney region or in the abdomen in 60% of the dogs at the time of diagnosis. Some dogs may have large renal masses, which extend from the dorsal to the ventral wall of the abdominal cavity, while others may have small to moderately enlarged, irregular renal masses attached to the dorsal abdominal wall (5). Abnormal size and shape of the kidneys as evaluated by abdominal radiography are usually seen in dogs at 8 to 9 years of age, but plain radiographs are not always sufficient to establish a

diagnosis of renal disease. If the clinical examination reveals typical skin nodules, repeated excretory urography and / or pneumoperitonography (Fig 2, 3) or computed tomography scans should if necessary be performed to confirm that the kidneys are affected (2, 29). Ultrasonographic examination of the kidneys will easily detect the cysts, but also tumour tissue on the inner surface of the cyst capsule may be seen (Fig 4) (5). Many cases of nodular dermatofibrosis reported in the literature have probably not received a diagnosis of renal cysts and neoplasms due to the lack of radiographic or ultrasonographic examination, of follow-up and of necropsy (2, 33).

The nodules of the skin are typically very firm, spherical to oval and usually small, ranging from 2-5 mm in diameter. The typical nodules are non-pruritic, located subcutaneously, and freely mobile to the underlying tissue. The predilection sites are all the limbs and the head region. In typical cases they are readily palpated, but may often be difficult to see. The age when the first nodules in the skin may be observed varies from 4 to 8 years, with a reported mean of 6 years (5). More than 200 nodules may usually be palpated in the skin at 8 to 9 years of age.

The size and number of tumours in the uterus varies considerably. Many dogs have small multiple leiomyomas that are not detected clinically (4). In a few dogs, large uterine tumours may be palpated, or the tumours are detected on abdominal radiographs or by computed tomography (5, 29).

Clinical pathology

A reduction in renal function and presence of renal metastases are the life-threatening consequences of the disease. The level of renal function is commonly evaluated by serum creatinine concentration as a measurement of glomerular filtration rate. Most dogs with renal cystadenocarcinomas will undergo a gradual decline in renal function and develop azotaemia, but a few dogs preserve their renal function until 9 to 10 years of age (4, 5). Although serum creatinine may be within normal reference values at 7 years of age, glomerular filtration rate as estimated by the more sensitive iohexol method may be reduced (34). The dogs had a normal glomerular filtration rate value during the first 5 years of life (Moe L and Lium B: in preparation). At the time of clinical diagnosis of renal cystadenocarcinomas (mean age of 8.2 years), the mean creatinine concentration of 54 dogs was 138 umol/L (normal reference values 75-110 umol/L) (Moe L and Lium B: in preparation).

Macroscopic haematuria is a common finding in renal tumours of humans (24). In dogs with renal cystadenocarcinomas, however, only 25% has macroscopic haematuria at the time of diagnosis (5), but occult blood in urine was much more

common. The majority of dogs had at least one positive dipstick urine-blood test during the course of the disease (Moe L and Lium B: in preparation). The frequency of bleeding from the lesions may possibly be at the same level in renal cystadenocarcinomas of dogs as in renal tumours in man, but because macroscopic bleeding occurs intermittently, it is more difficult for the owners to detect than for the human patients.

Prognosis, treatment and control

The median and mean age at death was 9.3 and 8.5 years, in two reports, respectively (4, 5). The most serious condition limiting the life span of the dogs, is the renal lesions and complications, including metastasis. Other causes of euthanasia are complications of nodular dermatofibrosis and dermatitis, and miscellaneous causes. It is uncertain whether the life span of the dogs is reduced compared with the normal life expectancy in German shepherd dogs. The mean survival probability after the diagnosis has been established, is relatively short, from 0.5 to 1.5 years (5), but the survival range is large, and some dogs may live with the diagnosis for 4 to 5 years (29).

No curative treatment has been found. Symptomatic treatment could be instituted against secondary disease such as the sterile peritonitis, dermatitis and renal failure. Unilateral nephrectomy may alleviate the symptoms if one large, non-functioning cystic kidney is present alongside with a functioning kidney (5). The syndrome is inherited, so can it be prevented by not using affected dogs for breeding (28).

Pathology

The typical gross appearance of the syndrome is enlarged, cystically distorted kidneys (Fig 5), numerous, whitish, firm skin nodules located in the subdermal or the subcutaneous tissue (Fig 6) and several tumours in the uterus of the bitches (Fig 7). The weight of the kidneys may vary from normal (95 g) to several kilograms, and the size of cysts and tumours from barely visible to several decimeters in diameter. Tumour tissue is commonly seen attached to the inner core of larger cysts. Both kidneys are always affected, but to a varying degree. In the renal cortex, multifocal hyperplastic to highly malignant epithelial proliferation is seen on histology. Sometimes ascites and hydrothorax may be present. The skin nodules consist of dense collagen fibres. In approximately 20% of the dogs, the collagen fibres in some nodules are dispersed by inflammatory cells. These inflammatory changes are believed to be the consequence of another skin condition such as chronic dermatitis superimposed on the nodular dermatofibrosis (Moe L and Lium B: submitted for publication). The uterine tumours consist of interlacing bundles of smooth muscle cells and are classified as leiomyomas. These tumours have not been recognised by other authors, possibly

because most case reports describe male dogs, and also because many bitches have not been submitted for necropsy.

Metastases (e.g. to sternal and abdominal lymph nodes, liver, lung, pleura, and peritoneum) from the renal carcinomas are found in almost 50% of the Norwegian dogs, but have not been reported to the same extent from other countries (4, 5, 6, 7, 16). This difference may be the result of the Norwegian cases being followed until an advanced stage was reached, and the performance of a necropsy in the majority of the Norwegian cases.

Small (1-3 mm) multifocal hyperplastic polyps have been found in the mucosa of the small intestine in some of the dogs (5, 8) The polyps are difficult to detect macroscopically and are easily missed due to autolysis if the necropsy is performed several hours after death. Polyps of the mucosa of the rectum have also been detected clinically (5). It has not been shown that the polyps are a consistent feature of the syndrome, but it may possibly be that most dogs have them at a certain age without giving apparent clinical signs.

Comparative aspects

Could the neoplastic syndrome in German shepherd dogs represent a valuable model for human disease? Several familial cancer syndromes in humans have been described (35, 36, 37, 38, 39, 40, 41, 42, 43, 44). Some of them are inherited in an autosomal dominant way. Hereditary renal tumours are described in humans without coexisting skin tumours: a) Renal cell carcinoma with a translocation involving chromosomes 3 and 8, b) von Hippel Lindau syndrome which is characterized by ovarian dysgerminoma, renal carcinoma and cysts, retinal tumour, nervous system tumours and cysts (but manifestations vary). The genetic defect has been characterized on chromosome 3.

A familial cutaneous collagenoma in humans has a clinical and histologic picture that is very similar to the nodular dermatofibrosis in dogs, but no internal malignancies are present (37).

There are heritable human syndromes in which benign skin tumours are markers for internal disorders or markers for internal malignancies. Examples of benign skin tumours associated with internal disorders are neurofibromatosis (which is characterized by cutaneous nodules, tumours of brain and peripheral nerves, sometimes renal neoplasms), and tuberous sclerosis (lipopigmented macules, adenomas, multiple fibromas, seizures, mental deficiency, some patients also: renal angiomyolipoma, renal cysts). Examples of diseases in which benign skin tumours are markers for internal malignancies include Cowden's disease (multiple trichilemmoma, fibroma, hamartoma, breast and thyroid cancer), and

Gardner's syndrome (epidermal and sebaceous cysts, dermoid tumours, fibromas and lipomas, and carcinoma of colon and rectum) (38, 39, 40, 42, 43, 44).

Although inherited tumours of the skin, kidneys and reproductive tract exist in humans (26, 35, 36), no exact parallel to the present multi-organ neoplastic syndrome is known in man. Even so, the study of the inherited DNA-abnormalities in German shepherd dogs with renal cystadenocarcinomas and nodular dermatofibrosis will give new information about the important role of genes in the pathogenesis of cancer. New diagnostic and therapeutic strategies could be explored. The interaction between the innate genetic constitution and the role of environmental factors on cancer development could be studied.

Future research
Several questions concerning the pathogenesis of the syndrome are under investigation. Some of the questions have been mentioned under previous headings. Tissue from spontaneous cases and from experimental dogs in a controlled population will be examined for morphological (immunhistochemical and electron microscopical) and chemical analysis. At the same time, DNA samples have been harvested both from renal tumour tissue and the skin nodules and DNA from leucocytes and other normal cells have also been sampled. Microsatellite analyses and gene analyses are currently being performed to unveil any genetic abnormalities involved. Another important target of future research is to produce a DNA test (or other methods) for the early diagnosis of the syndrome. There was no indication for a reduced penetrance, but more data are needed to conclude if there may be variable genetic expression.

References

1. Lium B, Moe L. Arvelig nyre- og hudkreft. En "ny" lidelse hos schäferhunder. (Hereditary renal and skin cancer. A "new" condition in German shepherd dogs). Schäferhunden 1983; 58: 16-23

2. Moe L, Lium B. Multiple bilaterale cystadenocarcinomer i nyrene hos schäferhund. Beskrivelse av et kasus med vekt på den røntgenologiske undersøkelse. (Multiple bilateral renal cystadenocarcinomas in the German shepherd dog. Description of a case emphasizing the radiographical examination). Nor Vet Tidsskr 1984; 96: 687-92

3. Moe L, Lium B. Hereditary multifocal renal cystadenocarcinomas and generalized nodular dermatofibrosis in the German shepherd dog. Abstracts of the 9th World Congress of the World Small Animal Veterinary Association, Hamburg: 1984: 244

4. Lium B, Moe L. Hereditary multifocal renal cystadenocarcinomas and nodular dermatofibrosis in the German shepherd dog: macroscopic and histopathologic changes. Vet Pathol 1985; 22: 447-55

5. Moe L, Lium B. Hereditary multifocal renal cystadenocarcinomas and nodular dermatofibrosis in 51 German shepherd dogs. J Small Anim Pract 1997; 38: 498-505

6. Krieger-Huber S, Faussner M. Nierenkarzinom und noduläre Dermatofibrose mit erblicher Disposition - Eine "neue" Erkrankung beim Deutschen Schäferhund. Kleintierpraxis 1985; 30: 235-42

7. Nilsson PO, Hellmén E, Hansson A. Multifokala cystiska njurcarcinom och nodulär dermatofibros hos schäfer. (Multifocal cystic renal carcinomas and nodular dermatofibrosis in German shepherd dog). Sven Vet Tidn 1985; 37: 377-80

8. Cosenza SF, Seely JC. Generalized nodular dermatofibrosis and renal cystadenocarcinomas in a German shepherd dog. J Am Vet Med Assoc 1986; 189: 1587-90

9. Bergström U. Multifokalt cystiskt njuradenokarcinom och nodulär dermatofibros hos schäfer. (Multifocal renal cystadenocarcinoma and nodular dermatofibrosis in the German shepherd dog). Sven Vet Tidn 1989; 41: 723-7

References

1. Lium B, Moe L. Arvelig nyre- og hudkreft. En "ny" lidelse hos schäferhunder. (Hereditary renal and skin cancer. A "new" condition in German shepherd dogs). Schäferhunden 1983; 58: 16-23

2. Moe L, Lium B. Multiple bilaterale cystadenocarcinomer i nyrene hos schäferhund. Beskrivelse av et kasus med vekt på den røntgenologiske undersøkelse. (Multiple bilateral renal cystadenocarcinomas in the German shepherd dog. Description of a case emphasizing the radiographical examination). Nor Vet Tidsskr 1984; 96: 687-92

3. Moe L, Lium B. Hereditary multifocal renal cystadenocarcinomas and generalized nodular dermatofibrosis in the German shepherd dog. Abstracts of the 9th World Congress of the World Small Animal Veterinary Association, Hamburg: 1984: 244

4. Lium B, Moe L. Hereditary multifocal renal cystadenocarcinomas and nodular dermatofibrosis in the German shepherd dog: macroscopic and histopathologic changes. Vet Pathol 1985; 22: 447-55

5. Moe L, Lium B. Hereditary multifocal renal cystadenocarcinomas and nodular dermatofibrosis in 51 German shepherd dogs. J Small Anim Pract 1997; 38: 498-505

6. Krieger-Huber S, Faussner M. Nierenkarzinom und noduläre Dermatofibrose mit erblicher Disposition - Eine "neue" Erkrankung beim Deutschen Schäferhund. Kleintierpraxis 1985; 30: 235-42

7. Nilsson PO, Hellmén E, Hansson A. Multifokala cystiska njurcarcinom och nodulär dermatofibros hos schäfer. (Multifocal cystic renal carcinomas and nodular dermatofibrosis in German shepherd dog). Sven Vet Tidn 1985; 37: 377-80

8. Cosenza SF, Seely JC. Generalized nodular dermatofibrosis and renal cystadenocarcinomas in a German shepherd dog. J Am Vet Med Assoc 1986; 189: 1587-90

9. Bergström U. Multifokalt cystiskt njuradenokarcinom och nodulär dermatofibros hos schäfer. (Multifocal renal cystadenocarcinoma and nodular dermatofibrosis in the German shepherd dog). Sven Vet Tidn 1989; 41: 723-7

10. Gilbert PA, Griffin CE, Walder EJ. Nodular dermatofibrosis and renal cystadenoma in a German shepherd dog. J Am Anim Hosp Assoc 1990; 26: 253-6

11. Vilafranca M, Fondevila D, Marlasca MJ, Ferrer L. Chromophilic-eosinophilic (oncocyte-like) renal cell carcinoma in a dog with nodular dermatofibrosis. Vet Pathol 1994; 31: 713-6

12. Perry W. Generalised nodular dermatofibrosis and renal cystadenoma in a series of 10 closely related German shepherd dogs. Aust Vet Pract 1995; 25: 90-3

13. Withrow SJ. Tumours of the urinary system. In: Withrow SJ, MacEwen EG, eds. Small animal clinical oncology. 2nd ed. Philadelphia: Saunders, 1996: 380-5

14. Guaguère E, Dandrifosse J-F, Delverdier-Poujade A, Mialot M, Magnol J-P. Dermatofibrose nodulaire chez le Berger Allemand: étude rétrospective de 10 cas. Prat Méd Chir Anim Compagnie 1996; 31: 211-7

15. Suter M, Lott-Stolz G, Wild P. Generalized nodular dermatofibrosis in six Alsatians. Vet Pathol 1983 ; 20: 632-4

16. Atlee BA, DeBoer DJ, Ihrke PJ, Stannard AA, Willemse T. Nodular dermatofibrosis in German shepherd dogs as a marker for renal cystadenocarcinoma. J Am Anim Hosp Assoc 1991; 27: 481-7

17. Bedu S, Héripret D. Un cas de dermatofibrose nodulaire du Berger Allemand. Prat Méd Chir Anim Compagnie 1994; 29: 487-91

18. Lium B, Svenkerud R. En eiendommelig type nyrecyster hos schæferhund. (A strange type of renal cysts in German shepherd dogs). Nor Vet Tidsskr 1978; 90: 567-9

19. Marks SL, Farman CA, Peaston A. Nodular dermatofibrosis and renal cystadenomas in a golden retriever. Vet Dermatol 1994; 4: 133-7

20. Baskin GB, De Paoli A. Primary renal neoplasms of the dog. Vet Pathol 1977; 14: 591-605

21. Priester WA, Mckay FW. The occurrence of tumors in domestic animals. Natl Cancer Inst Monogr 1980; 54: 22-51

22. Arnesen K, Gamlem HN, Glattre E, Moe L. Cancer epidemiology in dogs. Proceedings of the Fifth Nordic Symposium on Small Animal Disease, Oslo 1992: 113-8

23. Robinson FR, Garner FM. Histopathologic survey of 2,500 German shepherd military working dogs. Am J Vet Res 1973; 34: 437-42

24. Paulson DF, Perez CA, Anderson T. Cancer of the kidney and ureter. In: DeVita VT, Hellman S, Rosenberg SA eds. Cancer: principles & practice of oncology. 2nd ed. Philadelphia: Lippincott, 1985: 895-913

25. Paganini-Hill A, Ross RK, Henderson BE. Epidemiology of renal cancer. In: Skinner DG, Lieskovsky G, eds. Diagnosis and management of genitourinary cancer. Philadelphia: Saunders, 1988: 32-9

26. Gomella L, Stephanelli J. Malignancies of the kidney. In: Cameron RB, ed. Practical oncology. London: Appleton & Lange, 1994: 299-305

27. Klein MK, Cockerell GL, Harris CK, Withrow SJ, Lulich JP, Ogilvie GK, Norris AM, Harvey HJ, Richardson RF, Fowler JD, Tomlinson J, Henderson RA. Canine primary renal neoplasms: a retrospective review of 54 cases. J Am Anim Hosp Assoc 1988; 24: 443-52

28. Moe L, Lium B. Inheritance of renal cystadenocarcinomas and nodular dermatofibrosis in German shepherd dogs. In: Proceedings of the 7th Annual Congress of European Society of Veterinary Internal Medicine, Lyon: 1997: 101-3

29. Moe L, Lium B. Hereditary multifocal renal cystadenocarcinomas in German shepherd dogs: Computed tomography of the renal lesions. Vet Radiol Ultrasound 1997; 38: 335-43

30. Neugut AI, Robinson E. Multiple primary neoplasms. Cancer J 1992; 5: 245-8

31. Grantham JJ. Polycystic kidney disease: Neoplasia in disguise. Am J Kidney Dis, 1990; 15: 110-6

32. Truong LD, Krishnan B, Cao JTH, Barrios R, Suki WN. Renal neoplasm in acquired cystic kidney disease. [Review]. Am J of Kidney Dis 1995; 26: 1-12

33. Scott DW, Yager-Johnson JA, Manning TO, Walton DK, Johnson RP, Parker WM, Carman PS. Nevi in the dog. J Am Anim Hosp Assoc 1984; 20: 505-12

34. Moe L, Heiene R. Estimation of glomerular filtration rate in dogs with 99M-Tc-DTPA and iohexol. Res Vet Sci 1997; 58: 138-43

35. Li FP. Familial cancer syndromes and clusters. Curr Probl Cancer 1990; 14: 73-114

36. Taleisnik A. Malignancies of the skin. In: Cameron RB, ed. Practical oncology. London: Appleton & Lange, 1994: 133-43

37. Uitto J, Santa-Cruz DJ, Eisen AZ. Familial cutaneous collagenoma: genetic studies on a family. Br J Dermatol 1979; 101: 185-95

38. Hauck RM, Manders EK. Familial syndromes with skin tumor markers. Ann Plastic Surg 1994; 33: 102-11

39. Bunn PA, Minna JD. Paraneoplastic syndromes. In: DeVita VT, Hellman S, Rosenberg SA eds. Cancer: principles & practice of oncology. 2nd ed. Philadelphia: Lippincott, 1985: 1797-842

40. Parnes H, Miller J, Cameron, RB. Dermatologic problems and emergencies. In: Cameron RB, ed. Practical oncology. London: Appleton & Lange, 1994: 105-11

41. Colquhoun S. Malignancies of the soft tissues. In: Cameron RB, ed. Practical oncology. London: Appleton & Lange, 1994: 395-405

42. Webb DW, Clarke A, Fryer A, Osborne JP. The cutaneous features of tuberous sclerosis: a population study. Br J Dermatol 1996; 135: 1-5

43. Sampson JR. The kidney in tuberous sclerosis: manifestations and molecular genetic mechanisms. Nephr Dial Transpl 1996; 11, Suppl 6: 34-7

44. Cook JA, Oliver K, Mueller RF, Sampson J. A cross sectional study of renal involvement in tuberous sclerosis. J Med Gen 1996; 33: 480-84
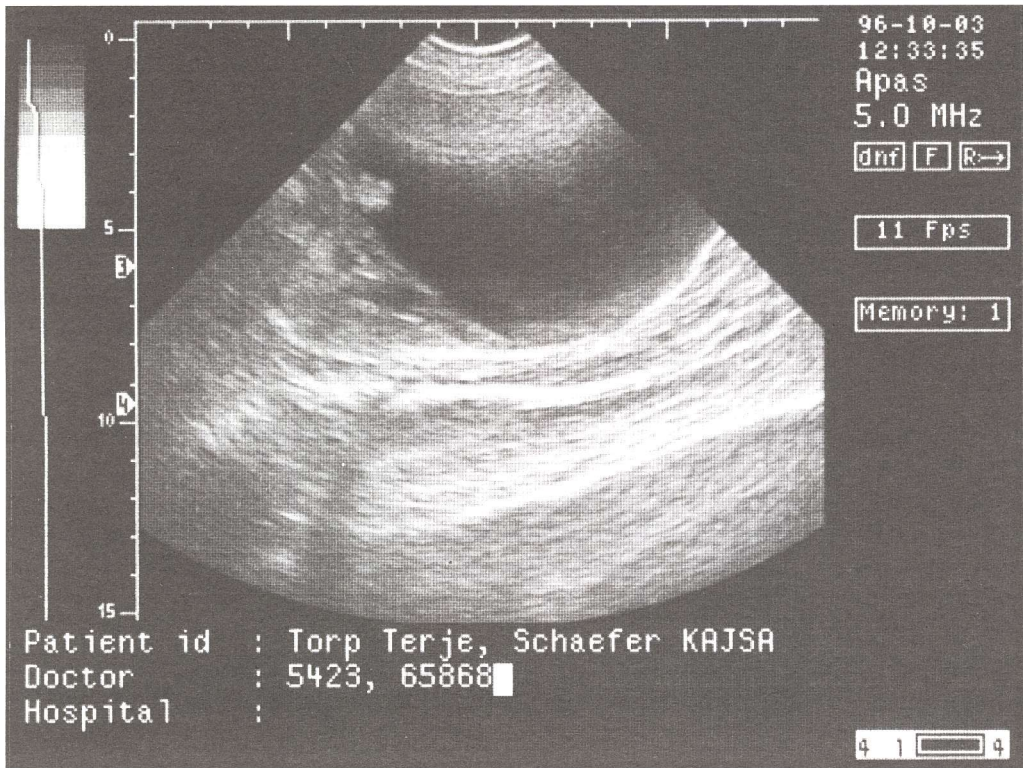
FIG 1.
German shepherd dog with nodular dermatofibrosis. Multiple small skin tumours can be seen on the shaved hind limb of an eight year old bitch.
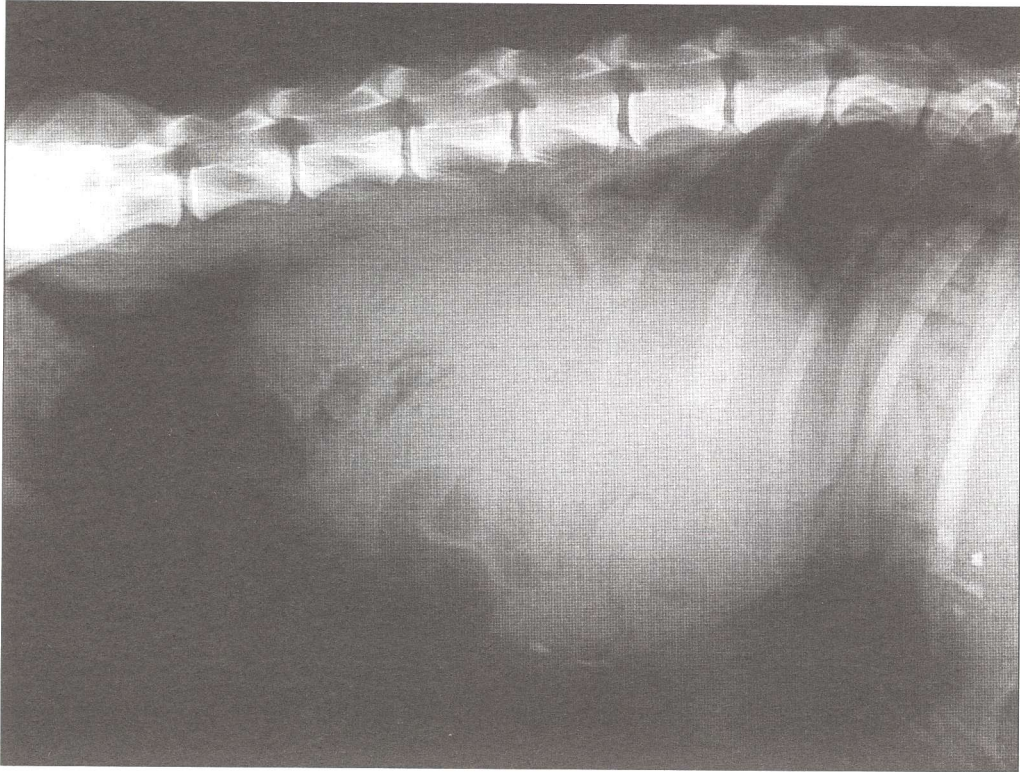
FIG 2.
German shepherd dog with renal cystadenocarcinomas. Abdominal radiograph of an eight year old bitch with artificial pneumoperitoneum showing a large mass occupying the abdominal cavity.
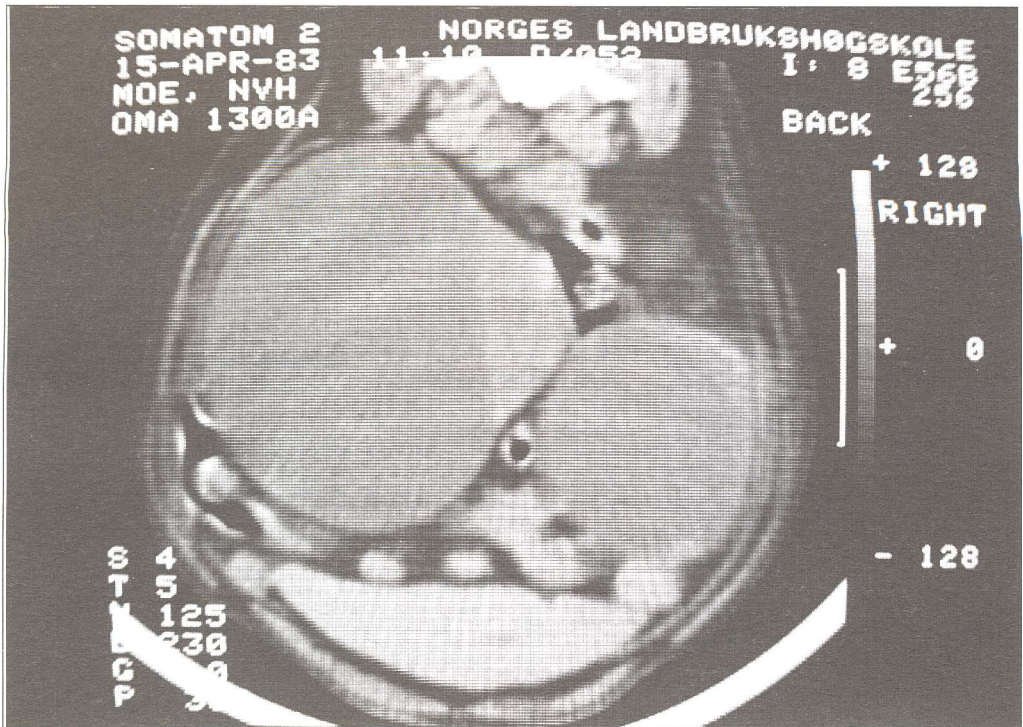
FIG 3.
German shepherd dog with renal cystadenocarcinomas. Computed tomographic image of the abdomen in a nine year old bitch with unequally enlarged kidneys containing cysts.
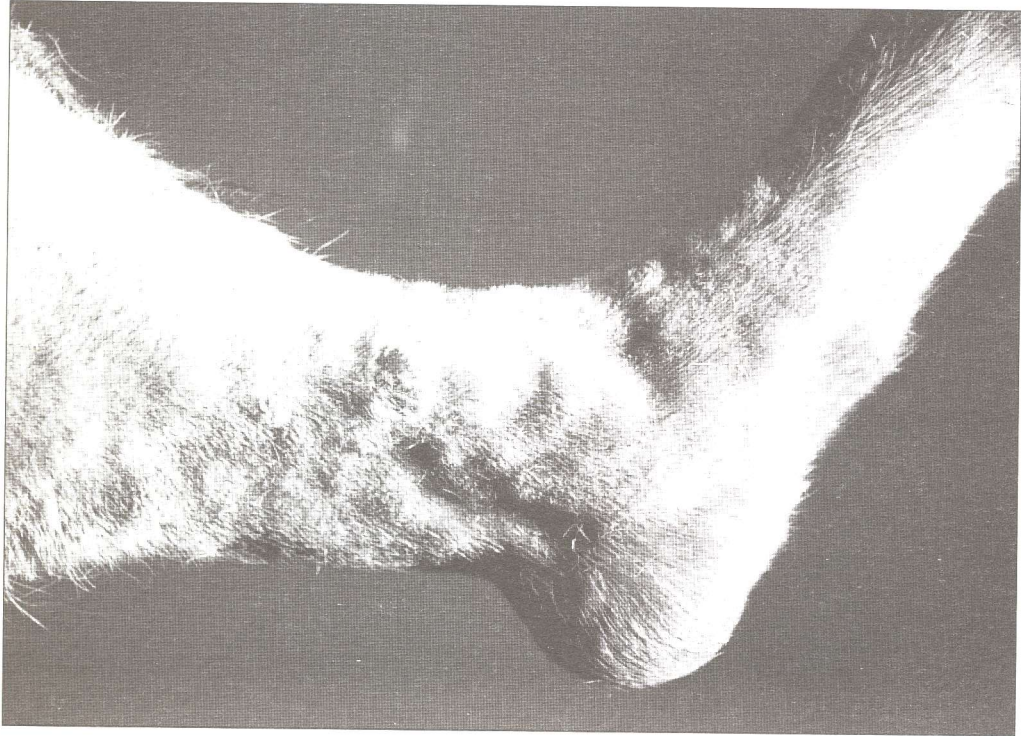
FIG 4.
German shepherd dog with multiple renal cystadenocarcinomas.
Ultrasonographic scan of an eight year old bitch showing a typical large cyst and
a tumour mass attached to the inner cyst wall that protrudes into the lumen.
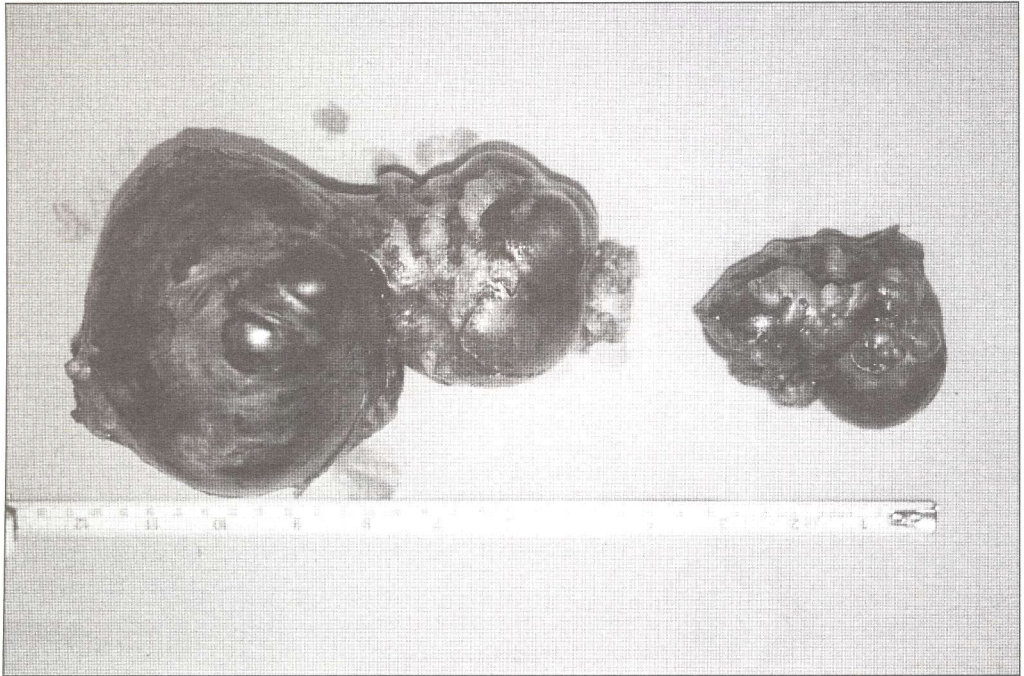
FIG 5.
German shepherd dog with renal cystadenocarcinomas. Macroscopic picture of an eleven year old bitch.
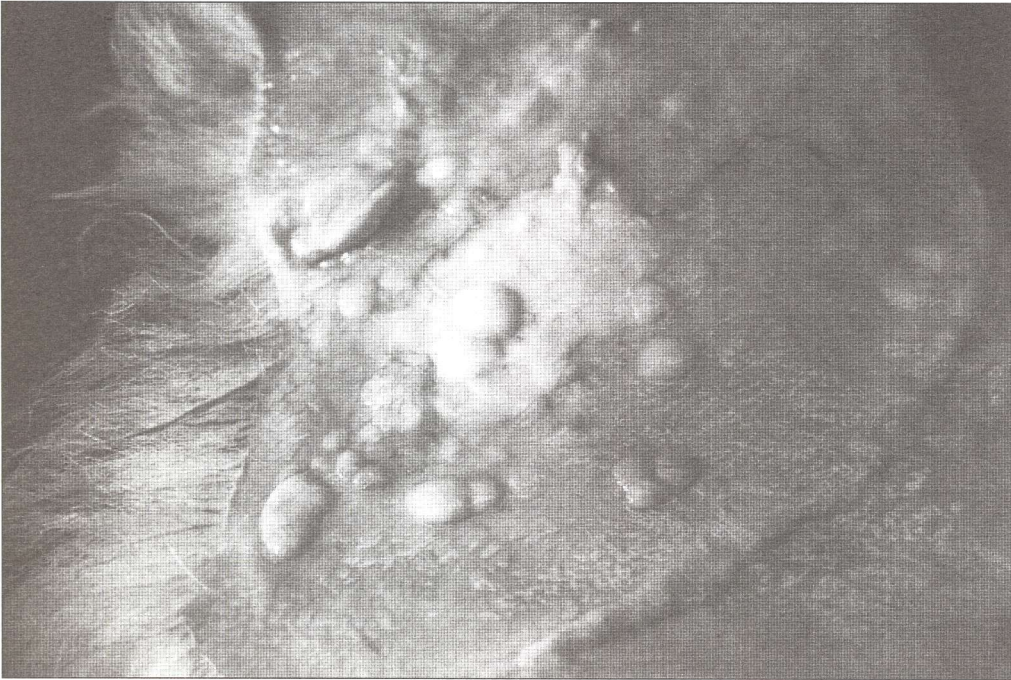
FIG 6.
German shepherd dog with nodular dermatofibrosis. The subcutaneous lesions of nodular dermatofibrosis are readily visible.
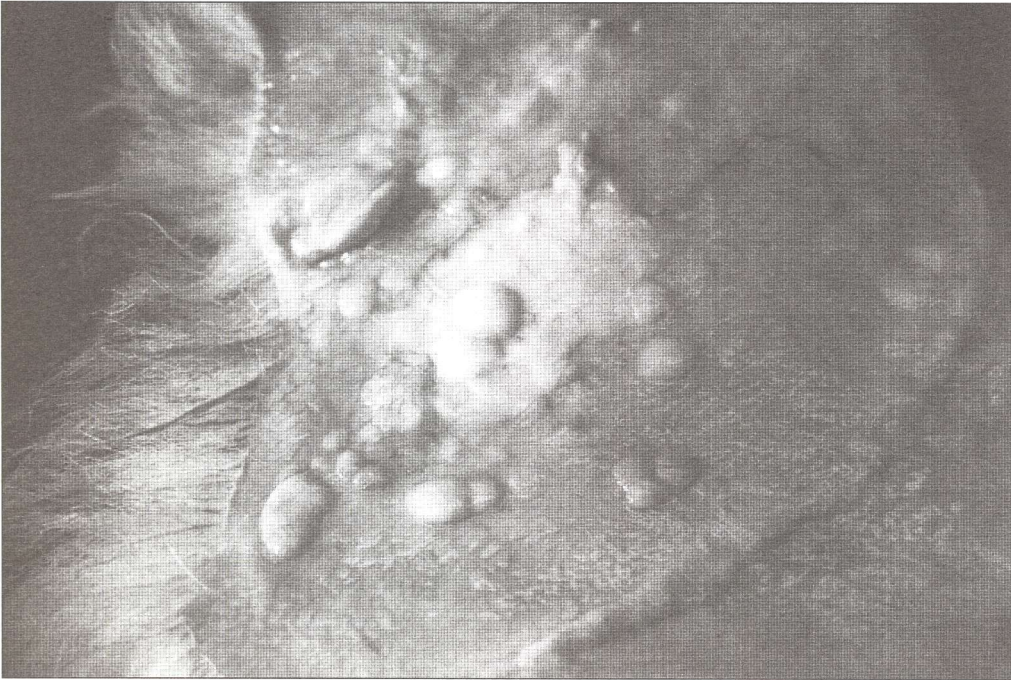
FIG 6.
German shepherd dog with nodular dermatofibrosis. The subcutaneous lesions of nodular dermatofibrosis are readily visible.

FIG 7.
German shepherd dog with uterine leiomyomas. Tumours of variable size and a concomitant mucometra are present in a seven year old bitch.