ACANTHOSIS NIGRICANS AND CANCER OF THE LIVER IN A DOG

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In 1936, one of the present authors (1), describing an example of benign acanthosis nigricans in a boy, expressed the belief that this disease in every instance—in the so-called benign as well as the malignant cases—shows a genetic relationship to certain forms of cancer.

Acanthosis nigricans is known to occur also in the dog. According to Tesseraux (2) 14 cases in that animal had been reported before 1930. It was thought that if acanthosis nigricans were observed in dogs in association with a glandular cancer, the conclusions derived from a study of human cases would be greatly strengthened. We are now able to report such a case. For this we are indebted to Dr. Charles E. Fletcher, veterinarian of New York City, under whose care the animal was, and who called our attention to the condition of the skin.

REPORT OF CASE

Dolly, a female German shepherd dog with some trace of Collie blood, was first seen in November 1936, at which time she was fourteen years old.

History: Dark pigmentation on the dog's flanks was first noticed at the age of two years, on the occasion of her first clipping.¹ The discoloration gradually spread over large

¹ The dog had spent all her life with the same people, who furnished us with all information.
areas of the body. At the age of ten years the animal aborted. At about the same time two large soft tumors became palpable on the left flank. These had not increased in size. In the past two years the roughness and darkness of the skin had progressed rapidly, and a disagreeable odor had developed.

Examination: Symmetrically distributed over large parts of the body, most markedly over the body-folds and on the hind-legs but also on the flanks and back, were many poorly circumscribed areas, varying in diameter from less than a centimeter to 7 or 8 cm., showing black, thickened, rough, hyperkeratotic skin (Figs. 1 and 2). The hair had not come off to any noticeable degree in these areas. The abdomen and nipples showed diffuse blackening and mild thickening. The anus also was involved. The odor of the dog was hardly bearable. On the left flank two smooth movable tumors could be felt in the subcutaneous tissues.
Histologic Examination: A biopsy was taken from the border of the lesion on the flank (November 1936). At the right side of the specimen (Fig. 3) the epidermis was thin, consisting of two to four layers of rete cells and a thin layer of granular cells, over which were many layers of horn cells. A moderate amount of pigment was present. The papillae were hardly visible. At the left side the epidermis showed long thick rete pegs extending down into the cutis. The papillae were long and the tips were covered with a malpighian layer of about six cells. The granular layer was absent in spots, and the surface of all the hypertrophied epidermis was covered by a thick, rather compact layer of horn cells containing many vesicular and rod-shaped nuclei. There was dense pigment in the basal layer and in processes of dendritic cells extending up into the rete. Some of the rete cells also contained
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much pigment, and there was yellow granular pigment in the parakeratotic scales. A few mitoses were visible in the basal layer.

The papillary layer showed some edema, a slight infiltration with round cells, and some large chromatophores. In the deeper corium, under both normal and thickened epidermis, were numerous cystic hair follicles filled with horny scales surrounding each hair.

The marked epidermal hypertrophy, hyperkeratosis, and pigmentation make this lesion similar to acanthosis nigricans in man. The parakeratosis and the dilatation of the hair follicles may be due to a difference in the reactivity of canine skin.

Diagnosis: Acanthosis nigricans; tumors of flank.

Course (May 1937): The skin condition was slowly progressive. The bad odor increased. The dog appeared listless, was without appetite, and lost considerable weight. On June 4, she was killed.

Autopsy (June 5): Externally the coat appeared shaggy and several areas of black, hyperkeratotic changes were present on the head near the nose and in other parts of the body. The eyes showed a thick mucopurulent discharge and conjunctivitis. The two non-adherent peach-shaped subcutaneous tumors on the left flank previously noted showed little change. One measured approximately 10 by 5 cm. and the other approximately 4 by 2 cm. Although there was some loss of weight, the musculature was essentially unchanged. Except for the lungs and the liver the gross pathological changes were slight.

The lungs showed areas of congestion and edema with emphysematous patches in the lower lobes. In the liver numerous firm whitish nodules, varying in diameter from 1 to 25 mm., were present, which on section yielded no fluid and gave no evidence of an inflammatory reaction (Fig. 4). The gallbladder was somewhat distended. The heart, spleen, pancreas, thyroid, and adrenals appeared to be normal. The kidneys were somewhat pale. A thorough examination of the intestines was made. The contents were scanty; no pathological changes were observed and no worms were found on gross examination. There was no evidence of neoplasm except for the multiple nodules in the liver and the subcutaneous tumors.

Histologic Examination: The specimen of skin examined (Fig. 5) did not show the diffuse thickening of the epidermis seen on biopsy, but projecting down from the surface epithelium and from the sides of the hair follicles were numerous processes, some finger-like, some branched, and others club-shaped. The cells stained normally with eosin and showed
practically no mitoses. Cells in the basal and adjacent layers showed an extraordinary amount of pigment. These processes were not unlike the elongated rete pegs which separate the enlarged papillae in some human cases. The parakeratotic masses on the surface and distending the hair follicles were more marked than in the biopsy specimen. One of the plugged follicles contained pus and was surrounded by a small abscess. Edema and lymphocytic infiltration were present throughout the papillary layer.

The adrenals appeared normal.

The ovaries showed some evidence of fibrosis.

The subcutaneous tumor was a lipoma.

Sections of the lung showed diffuse edema and small patches of anthracosis.

Sections of the kidney showed congestion and cloudy swelling of tubules. There was some exudation of serum about the glomerular tufts.

Sections of the liver showed numerous small and large neoplastic masses. The smaller consisted of cords of one or two rows of polygonal cells lying in a dense fibrous stroma, often adjacent to a portal vein. The tumor cells were smaller than those of the liver parenchyma. Their protoplasm stained densely and was slightly basophilic. The nuclei were small, nearly round, and often eccentric. They stained deeply but showed a distinct wall and some chromatin network. No mitotic figures were seen in the cords. The larger nodules (Fig. 6) were made up of larger cords and nests of similar cells—often twenty cells in width. Most of them stained densely and evenly but a few were finely vacuolated. The cells were often palisaded at the edge of the cords but formed no true tubules. The nests and cords were separated by a delicate connective-tissue network. In Foot-Bielschowsky preparations no reticulum was seen within the groups of epithelial cells.

The tumor cells showed little similarity to those of the liver cords or bile ducts. They resembled rather those seen in carcinoids of the appendix. A Fontana stain, however, failed to show any argentaffine granules.

Where the neoplasm adjoined the liver parenchyma, there was no evidence of encapsulation. In a few areas there were accumulations of lymphocytes and plasma cells, but elsewhere no inflammatory reaction was observed.
The histologic picture leaves little doubt that this tumor was a carcinoma, and as no origin could be found elsewhere, it seems probable that it was primary in the liver. The fact that the nodules were multiple and that the growth did not invade other organs does not exclude such a diagnosis.

Kaufmann (3) mentions multiple nodular carcinoma as a form of primary tumor in human beings and states that metastasis is relatively rare. Hutyra, Marek and Manninger (4) mention primary adenocarcinomata of the liver in dogs occurring in multiple firm nodules of varying size. They cite Jost, who found that primary cancer of the liver is comparatively more common in animals than in man and often develops in the form of adenomatous carcinoma. Poinsot (5) describes primary cancer of the liver in dogs with multiple nodules. One of Ball's dogs, according to Poinsot (5), showed several of these round white firm nodules. Merillat (6) states that in canine carcinoma of the liver metastatic foci are exceptional. The tumors frequently grow to large size and persist indefinitely without forming secondary foci. Moreover, dogs with these tumors rarely develop cachexia.

The diagnosis in the present case, therefore, is multiple hepatic adenocarcinomata; acanthosis nigricans with abscess formation; edema of lungs; lipomata of skin. Acanthosis nigricans was present from at least the second year of life. The duration of the cancer of the liver is a matter of conjecture.

Among the many human cases of acanthosis nigricans and cancer, Case 2 of Masson and Montgomery (7) showed a similar tumor. The patient was a man of thirty with acanthosis nigricans and abdominal pain of two months' duration. Four months later a laparotomy revealed multiple nodules of the liver showing adenocarcinoma of Grade 1. A primary tumor elsewhere could not be found. The patient died four months later. An autopsy was not performed.

Identity of Canine and Human Acanthosis Nigricans

There is still some difference of opinion as to whether acanthosis nigricans in man and in dogs is the same process. Doubt of the identity of the canine and the human disease seems to arise chiefly from the fact that cancer, so often seen together with acanthosis nigricans in man, has rarely been observed in the canine cases (Henry and Bory, 8; Nörr, 9; Heller, 10). There is, however, beside our case, one other reported by Schindelka (11) and Habacher (12) in which cancer occurred in association with acanthosis nigricans in a dog. This was a medullary carcinoma of the thyroid gland, with metastases in lung, liver, kidneys and lymph nodes. Other cases may well have been overlooked, as in most reports of acanthosis nigricans in the dog there is no mention of x-ray examination, operative investigation, or autopsy.

It must be admitted that there exist some differences between acanthosis nigricans in human beings and in dogs. In dogs the histologic picture seems to vary somewhat; the soft verrucous outgrowths so often associated with the human lesions are rarely seen. Habacher (12) and Henry and Bory (8) state that dogs do not show marked hyperkeratosis or papillary hypertrophy. In our case, on the other hand, more hyperkeratosis was present than is common in man, and the papillary hypertrophy was very definite, comparable to that
observed in Schindelka's (11) case. Secondary inflammatory reaction seems to be more pronounced in dogs.

Authors disagree as to the condition of the hair. Loss of hair in involved areas is reported by Schindelka (11), Schlenker (13), and Fechner (14). The dog described in this paper did not show any grossly denuded areas, though in sections there was evidence of some loss of hair. Differences as to the condition of the hair appear also in reports of acanthosis nigricans in man: most authors report loss of hair while in the case reported by one of us (H. O. C., 1) the normal amount of hair was present in the involved axillae.

Milks (15) and Hutyra, Marek and Manninger (4) point to the difference in pigment distribution. In the dog they observed pigment in the papillary body around the blood vessels and glands as well as in the epidermis. Henry and Bory (8) go so far as to create a new name, dermatose lichenoid pigmentaire marginée for the skin disease in dogs and separate the condition from acanthosis nigricans. Their "marginal zones," by the way, were absent in our case.

These differences do not seem great when we consider how much the skin of the dog differs from that of man in structure and in response to various stimuli. On the other hand, the similarities in location, course, clinical and histological picture point to a single skin disease affecting the two species. This is the opinion also of Michy (16), Habacher (12), and Tesseraux (2).

In dogs the endocrine disturbances which are reported as accompanying acanthosis nigricans (Fantin, 17; Lanfranchi and Seren, 18; and Fechner, 14) are even vaguer than the manifold and rather contradictory endocrine symptoms described in human beings with the disease. In none of the canine cases is a systematic endocrine examination of the sick dog or a thorough follow-up recorded.

**RELATIONSHIP OF ACANTHOSIS NIGRICANS TO CANCER**

The study of cancer in dogs presents many difficulties. Family histories which might establish an hereditary influence are almost impossible to obtain. Careful examinations, x-ray pictures, and autopsies are naturally scarce. Moreover, relatively few animals reach the cancer age (Jackson, 19).

Though our knowledge of tumors in domestic animals is limited, cancer seems to be quite frequent among them. The evidence strongly suggests the dog as the most susceptible of the domestic animals to neoplastic proliferation (Feldman, 20). Among aged dogs especially there seems to be a high incidence of the disease (Mayo, 21; Feldman, 20; Jackson, 19). While cancer of the gastro-intestinal tract in dogs is extremely rare (Rubarth, 22) and cancer of the stomach is practically unknown (Jackson, 19), cancer of the liver is not uncommon (Formad, 23). Medullary cancers especially are fairly frequent in old animals (Formad, 23). We must, therefore, consider the possibility that the existence of cancer in our dog was a mere coincidence.

Statistics compiled by Moncorps in 1931 (24) and the cases recorded since show an incidence of cancer of about 50 per cent in human patients with acanthosis nigricans. This frequency of association and the fact that the two diseases often appear at the same time and run a parallel course force the as-
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sumption of some etiologic relationship. Moreover, as one of us has shown, the type of cancer found in "malignant" acanthosis nigricans is rather frequently recorded in the antecedents of human juvenile cases. These facts together with the clinical and probably also the etiologic identity of the "benign" and "malignant" forms of acanthosis nigricans, and the variation of the chronologic sequence of acanthosis nigricans and cancer in the various cases, suggest a genetic relationship between the two diseases.

The observation of a second instance of canine acanthosis nigricans associated with glandular carcinoma is merely a link in the chain of evidence indicating an etiologic relationship between the two lesions.

CONCLUSIONS

A case of acanthosis nigricans and carcinoma of the liver in a dog is described. Acanthosis nigricans in dogs and human beings is essentially the same process. The observation recorded is another instance of the association of acanthosis nigricans and a glandular cancer, and is at least consonant with the hypothesis that there is a common genetic factor for acanthosis nigricans and the cancer.

BIBLIOGRAPHY

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