ACANTHOSIS NIGRICANS: AN ANALYSIS OF DATA IN TWENTY-TWO CASES AND A STUDY OF ITS FREQUENCY IN NECROPSY MATERIAL[1]

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Acanthosis nigricans is a result of a poorly understood reaction of the skin to underlying metabolic faults. These metabolic errors, which must be considered in the broadest sense, have been but little investigated in the past. This study was undertaken with two thoughts in mind: 1) to analyze the cases of acanthosis nigricans encountered at the clinic and 2) to analyze the histopathologic features of axillary skin removed at necropsy after death from malignant and nonmalignant disease, in an effort to determine, if possible, the incidence of acanthosis nigricans in patients without recognized signs and symptoms of this disorder. It was hoped that new knowledge would be gained concerning this condition which, while rare, has obvious fundamental importance in the pathogenesis of pigmentary disorders and malignant disease.

The literature has been reviewed extensively by Moncorps (1) and more recently by Curth (2). To their reviews there is little to be added.

Twenty-two cases of unqualified acanthosis nigricans have been encountered at the clinic, of which thirteen were reported previously by Masson and Montgomery (3). In the majority of these cases confirmation of the clinical diagnosis was made by histopathologic examination of material removed for biopsy. Eleven patients had the adult type, or that secondary to malignant disease, while eleven had the juvenile or benign type.

For the purpose of clarity these two types will be discussed separately, although the clinical and histopathologic features of acanthosis nigricans are identical in both forms.

The essential data concerning the eleven patients with the adult or malignant type of acanthosis nigricans are given in table 1. In five of these patients the signs and symptoms referable to the skin were the primary complaint and the reason for examination at the clinic. Two other patients were referred for examination for malignant disease because of the recognition of acanthosis nigricans elsewhere. In two others, acanthosis nigricans had not been observed by the patients.

The degree of cutaneous involvement by the lesions of acanthosis nigricans varied to a great extent. The disease was always present in the axillae; the crural region and sides of the neck were next in frequency. In three patients almost the entire integument was affected. In two patients the palms and soles were keratodermic and in four patients the tongue and buccal membranes were involved. A sore tongue and mouth, to the extent of interfering with eating, were noted in two cases.

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As noted from table 1, symptoms of acanthosis nigricans, for the most part, appeared before or at the same time as the symptoms of malignancy. In two

TABLE 1

Adult (malignant) acanthosis nigricans

CASE	AGE (YRS.) AND SEX	DURATION BEFORE ADMISSION (MOS.)		DEATH (MOS.) AFTER ADMISSION	MALIGNANCY		REMARKS
		Acanthosis nigricans	Malignant symptoms		Type	Familial	
1	56M	6	3	3	—	Pos.	Malignant death. Negro
2	38M	15	24	8	Carcinoma, stomach; metastasis	Neg.	
3	64F	3	None	21	Adenocarcinoma, gr. 2, uterus	Pos.	Exam. neg. for malignancy 3 mos. before exploratory operation
4	30M	2	5	No data	Primary adenocarcinoma, liver	Pos.	
5	29M	5	None	4	—	Neg.	Abdom. exploration neg. Malignant death, root pain
6	40M	?	4	—	Lymphoblastoma, chest*	Neg.	Acanthosis nigricans discovered in exam. Pulmonary findings improved after roentgen therapy
7	71M	24	24	9	—	Neg.	Large abdominal mass extrinsic to G.I. system and kidneys
8	66F	6	None	1	Gr. 3 adenocarcinoma, ovarian Virchow's node	Pos.	Died pulmonary embolism after biopsy of Virchow's node
9	39M	1½	None	5	—	Neg.	Gastric ulcer 1 yr., malignant death, root pain
10	25M	?	6	7	Lymphosarcoma, stomach; metastasis	?	Root pain
11	52M	24	24	16	Inoperable carcinoma, stomach*	Neg.	

* Diagnosis by roentgenologic examination.

patients the only evidence of malignancy in the history was unexplained loss of weight. In four patients there were no symptoms on which to base a diagnosis

of malignancy. A severe degree of root pain was a terminal event in three of the eleven patients.

The total duration of acanthosis nigricans varied from six and a half to forty months; but in only two patients was it longer than twenty-four months. Only one patient is alive (case 6) and he was first seen in November, 1946. One other patient died of a pulmonary embolus while the other nine patients died of their malignancy or had a malignant type of course prior to death. All but one patient died elsewhere and no necropsies were performed.

A familial background of malignancy has been strongly emphasized by Curth (2). Such a background was present in four of our cases and questionably so in one other.

Also eleven patients with the benign juvenile type of acanthosis nigricans have been seen (table 2). Four were males and seven were females. To our knowledge only one of these patients has died and the cause of death was unrelated to acanthosis nigricans. Only two patients have had acanthosis for less than five years and, unfortunately, further observation has been impossible in these two.

The degree of cutaneous involvement by the lesions of acanthosis nigricans never reached the extent in this benign type that was attained in the malignant form. The lips, tongue, buccal membranes and the distal part of the extremities were involved in no patient and even the areas of predilection did not assume the extreme degrees of pigmentation and epidermal hyperplasia seen in the malignant variety.

Of immediate interest is the association of acanthosis nigricans with endocrine disturbances of various types. Only three patients had no evidence of endocrine disturbance and these were males. All the females had some glandular dysfunction or disturbance. Only one patient had a familial background of carcinoma. The presence of cancer in the background of these patients is not found with the frequency obtained in the previously discussed cases of the malignant variety of acanthosis nigricans. Familial diabetes was present in two cases.

In three women there was evidence of severe endocrine dysfunction consisting of amenorrhea, hirsutism and obesity with other changes noted in table 2. The criteria for the diagnosis of Cushing's syndrome, arrhenoblastoma and tumor of the adrenal cortex were not fulfilled completely; yet there was sufficient evidence of adrenal tumor in two patients to warrant exploratory operation. This was done without positive pathologic findings.

As far as could be determined the acanthosis nigricans in this group remained unchanged without progression or regression of the cutaneous lesions or pigmentation.

The second part of this study dealt with the endeavor to find the proportion of patients who had histologic evidence of acanthosis nigricans. Specimens of axillary skin were obtained at necropsy in eighty-nine cases, in thirty-five of which primary or metastatic malignant lesions of the abdominal and thoracic cavities were found. In the remaining fifty-four cases death resulted from multiple causes but none from a demonstrable malignant process; these cases

TABLE 2

Benign juvenile acanthosis nigricans

CASE	AGE (YRS.) AND SEX	DURATION ACANTHOSIS NIGRICANS BEFORE ADMISSION (YRS.)	ENDOCRINE DISTURBANCE	OTHER PATHOLOGY	COURSE	FAMILIAL CANCER OR ENDOCRINE DISTURBANCE	REMARKS
12	24F	24	Adenoma, thyroid	—	9 yrs. later no change	—	1 sister, same condition less pronounced
13	29F	10	Obesity	—	13 yrs. later no change	—	1 child, calcinosis cutis
14	16M	2	Latent diabetes, obesity	—	—	Diabetes	
15	30F	7	Obesity, amenorrhea, sterility, hirsutism	—	No change menses 2-3 mos.	—	Exploration, adrenals normal
16	19M	1+	—	Duodenal ulcer, obstr.	—	—	No answer to follow-up
17	23F	8	Exophthalmic goiter. Polyglandular disturbance?	Essential hypertension, latent syphilis	—	—	Died 3 yrs. later, bacteriemia
18	13F	12	Obesity	—	No change	—	
19	50M	30+	—	Hypertension	—	—	
20	30M	5+	—	—	—	Carcinoma	No answer to follow-up
21	25F	10	Obesity, hirsutism, masculine type, small breasts, congenital absence of vagina	—	No change	—	17 ketosteroids 13.5 mg. in 24 hrs.
22	26F	?	Hirsutism, obesity, amenorrhea, voice change, epigastric pain, headache	—	5 yrs. later no change	Diabetes	Exploration, adrenals normal. 17 ketosteroids 13.1 mg. in 24 hrs.

were considered as controls. No patients in this group of eighty-nine had clinical evidence of acanthosis nigricans and none were seen in the section on dermatology.

Histologic evidence (4) of acanthosis nigricans in the specimen of axillary skin was present in one case in the control group.[2] This patient was a girl twenty years of age who died of thrombocytopenic purpura of three weeks' duration. Nothing that suggested acanthosis nigricans was noted in the history or on examination, yet the microscopic findings were considered diagnostic. It is possible that this is an example of an unrecognized mild form of the benign juvenile type of acanthosis nigricans.

The specimen of axillary skin in only one case revealed histologic evidence of acanthosis nigricans among those cases in which death had been associated with malignant disease. The microscopic findings, while definite, were minimal, and consisted of moderate hyperkeratosis, slight acanthosis with spotty areas of atrophy and some increase of melanin pigmentation (4). The review of the findings at necropsy in this case revealed a carcinoma of the right kidney without evidence of metastasis. No involvement of the adrenals or paraganglia was found. The patient was seventy-five years of age and died of bronchopneumonia in a state institution.

In this series there were eight cases of carcinoma of the stomach, four cases of carcinoma of the sigmoid and three of the breast, two each of carcinoma of the kidney, prostate, cecum and pancreas, one each of the ovary, perineum, Bartholin gland, lung, rectum, gallbladder and urinary bladder. Sarcoma was present in two cases, melanoma in one, lymphosarcoma in one and carcinoid in one.

The study of microscopic sections of skin disclosed findings of particular interest in both groups of necropsy material. A pattern of epidermal folding was present in many sections. In addition a minimal degree of spotty acanthosis related often to the follicles, with evidence of moderate hyperkeratosis and occasional areas of atrophy was seen. These changes combined with the presence of small amounts of pigment as shown by stains for melanin were highly suggestive of the microscopic features of early acanthosis nigricans. However, such changes were seen without difference and incidence in the two groups of patients, especially in those patients past forty years of age. It is felt that these changes must be considered normal in the skin of this area (5). The amount of melanin pigmentation was distinctly less in these sections than in sections of classical acanthosis nigricans.

COMMENT

Acanthosis nigricans has been thought to exist far more frequently than it has been diagnosed. Yet it is an admittedly uncommon disorder. It was with the thought that some idea of its frequency could be obtained that this study

[2] Dr. Hamilton Montgomery kindly reviewed and confirmed the microscopic diagnosis.

was undertaken. Even when histopathologic criteria for the diagnosis of acanthosis nigricans are used, this dermatosis is rarely observed as it was found only once in a series of thirty-five patients in whom the primary or metastatic lesions of cancer were present in the abdomen or thorax. This series is too small to be used as a basis for determining the true incidence of acanthosis nigricans in patients with malignant disease.

The association of acanthosis nigricans with malignancy and with the hereditary aspects of cancer have been reviewed extensively in the past. These factors are reflected in this series, yet no new information can be added to our small knowledge of this condition.

No instance of metastasis of a malignant lesion to the axillae was found in any microscopic section. It is felt that the finding of lymphosarcoma in a specimen removed for biopsy in a case of acanthosis nigricans reported by Nicholas (6) was coincidental.

The combination of endocrine disorders with acanthosis nigricans also has merited attention in the past; this association again is seen in this series of eleven patients with the benign juvenile form.

Too little is known to permit comment on the pathogenesis of acanthosis nigricans with any certainty of the correct answer. The frequently incriminated involvement of the chromaffin system by malignant infiltration or pressure does not satisfy the requirements. That the endocrine system and that carcinoma play prominent parts cannot be denied, yet the exact relationship is still remote.

The chemical relationship of epinephrine, tyrosine, phenylalanine and melanin (7), the acanthotic and pigmentary principle of estrogens (8, 9), the hypertrophic gingivitis and hypertrichosis produced by certain drugs, and the influence of vitamin C and other factors provide much material for further investigation. It would appear that a product of the endocrine glands and of malignant tissue, chemically the same or similar, is necessary to produce this pigmentary and acanthotic dermatosis.

SUMMARY

The data on twenty-two cases of acanthosis nigricans have been reviewed and the salient features presented. Eleven cases were of the type associated with malignant disease while another eleven cases were of the benign juvenile type.

In an attempt to determine the incidence of acanthosis nigricans by histopathologic study, specimens of axillary skin were obtained at necropsy in fifty-four cases of nonmalignant disease and in thirty-five cases of malignant disease. In each group there was one case in which there was histologic evidence of acanthosis nigricans. It is doubtful, however, that this represents a true incidence of the disorder.

The close similarity of the histologic features of early acanthosis nigricans and normal axillary skin are discussed briefly.

The etiology and pathogenesis of acanthosis nigricans are not yet known.

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