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1

Acanthosis Nigricans and Adenocarcinoma

(*Malignant or Adult Acanthosis Nigricans*)

Though Pollitzer (35) and Janovsky (24) independently described acanthosis nigricans in 1890, it was Pollitzer (35), in 1909, who made the first extensive study of cases previously reported and who emphasized the relationship of the skin disease to abdominal malignancy. During the next 50 years, over 750 cases were reported, about half of which were associated with adenocarcinoma, principally of the stomach. Several excellent surveys have been carried out (4,25,30,32); probably the greatest contributions have been the numerous and extensive studies of Curth (7–15).

Acanthosis nigricans has been divided into three categories: (*a*) benign, which may be present at birth or may begin later, either in childhood or, more often, at puberty, at which time it becomes more active (this type is often associated with endocrine disorders, especially Cushing's syndrome) (7,12); (*b*) pseudo, seen in brunettes and associated with and dependent upon obesity; and (*c*) malignant, which almost always arises in persons over twenty years of age and is always associated with an internal malignant tumor (14). The benign and malignant types occur with about equal frequency. A similar condition occurs in animals (8,38).

Genetic studies on acanthosis nigricans have revealed that only the benign type shows a familial incidence and that a dominant inheritance pattern is most common (7,18,21). The discussion that follows will be concerned largely with the malignant, or adult, type.

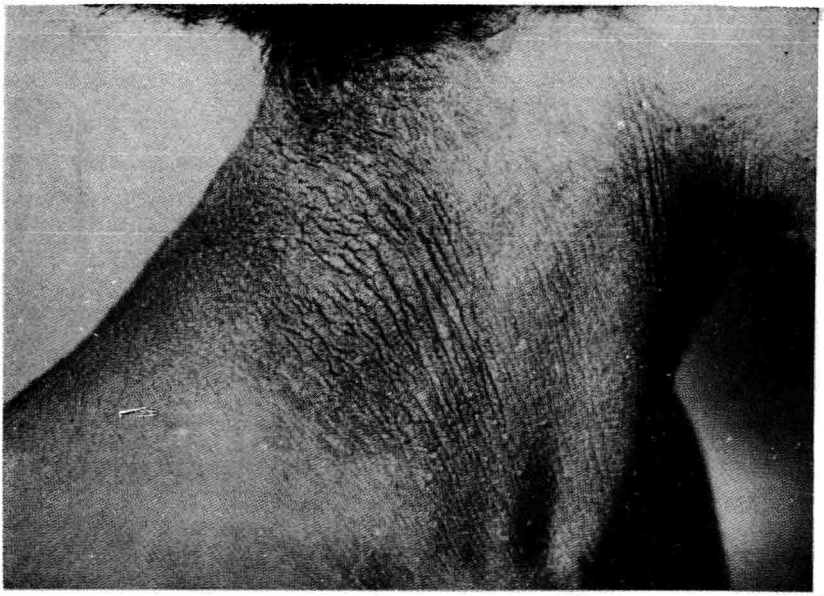

FIG. 1-1. *Acanthosis nigricans—malignant form.* Pigmentation and papillomatosis of cervical region associated with gastric adenocarcinoma. (*Courtesy of H. O. Curth, New York, N.Y.*)

Of special interest is the report of Knapp (25) that acanthosis nigricans is of viral etiology.

SYSTEMIC MANIFESTATIONS

Skin: Involvement of the skin may precede, accompany, or follow the detection of the cancer. It parallels the cancer in proportion to the degree of spread; it may regress with irradiation therapy or surgery of the tumor and may reflourish with recurrence of the adenocarcinoma (12,14).

In approximate order of frequency of pigmentation and papillomatous changes are the axillas, neck, genitalia and other flexural surfaces, umbilicus, and areolas. In addition to these changes, there is an exaggeration of normal skin markings. The axillas or neck usually become pigmented before other areas are involved (Figs. 1-1,1-2). Palmar and plantar hyperkeratosis may accompany the other changes (1,40). More than 80 percent of the affected persons are over forty years of age at the onset (27).

Microscopically, the skin exhibits the following features: increased thickness of stratum corneum, irregular acanthosis and atrophy of stratum spinosum, elongated, narrow papillary bodies, dense melanin deposits in the basal layer, and a few pigment-laden chromatophores in the

papillary bodies (31). Increased numbers of mast cells may also be seen in the corium.

Adenocarcinoma: Curth (12,14) presented clear-cut evidence that nearly all associated tumors are adenocarcinomas. Furthermore, she (7, 8–10) indicated that 92 percent of these tumors arise in the stomach (about 60 to 65 percent) or abdominal cavity (14,18,32). The uterus, ovary, gallbladder, pancreas, and intestine may also be the primary site, in approximately that order. The other 8 percent arise in the breast, lung, etc.

Adenocarcinoma associated with acanthosis nigricans is extremely malignant. The mortality rate is 100 percent, and the average survival period after discovery is 9 to 12 months.

Oral Manifestations: Possibly the earliest description of oral lesions in acanthosis nigricans was made by Pollitzer (34) in 1909. Since then numerous authors have mentioned the occurrence of oral involvement, but, in most cases, description has been meager. Masson and Montgomery (27) suggested that at least 50 percent of patients with the adult form have oral lesions; Bogrow (4) noted an even higher rate of occurrence. Fladung and Heite (18) suggested an incidence of oral involvement of 53 percent. (It is interesting that they also found a 23 percent incidence of oral lesions in the benign form of acanthosis nigricans.) On the other hand, the present authors, on the basis of a survey of over 200 reported malignant cases, think that a truer value is probably about 30 to 40 per-

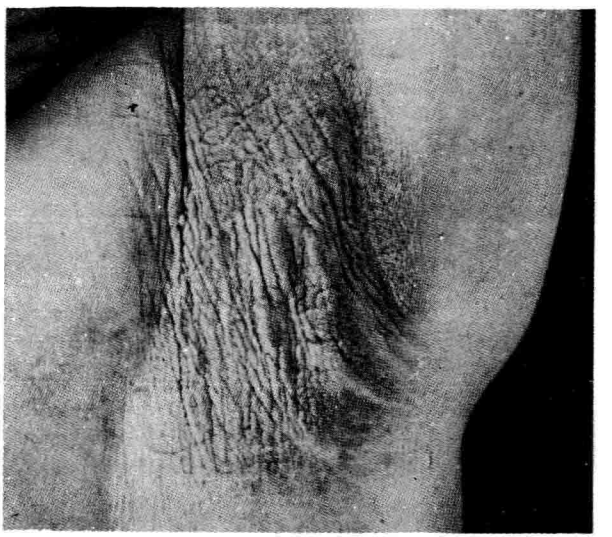

FIG. 1-2. Pigmentation and papillomatosis of axillary area associated with gastric adenocarcinoma.

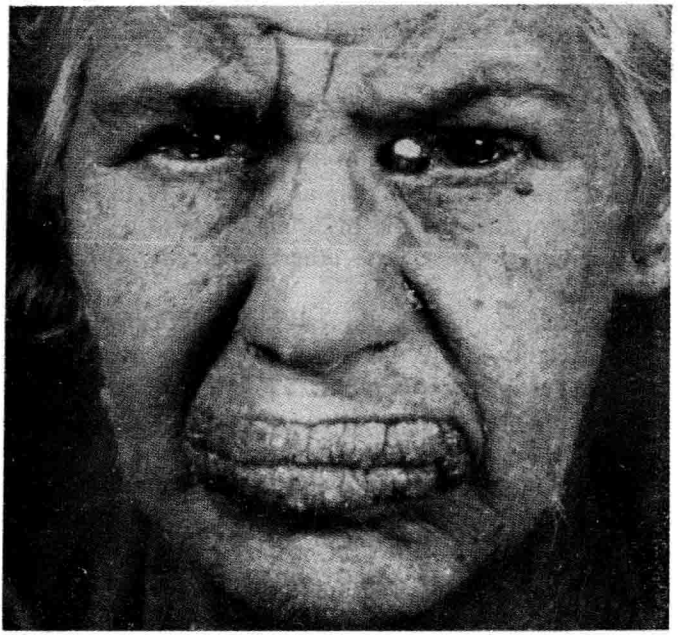

FIG. 1-3. Papillomatosis of lips associated with gastric adenocarcinoma. Also note conjunctival papillomatosis.

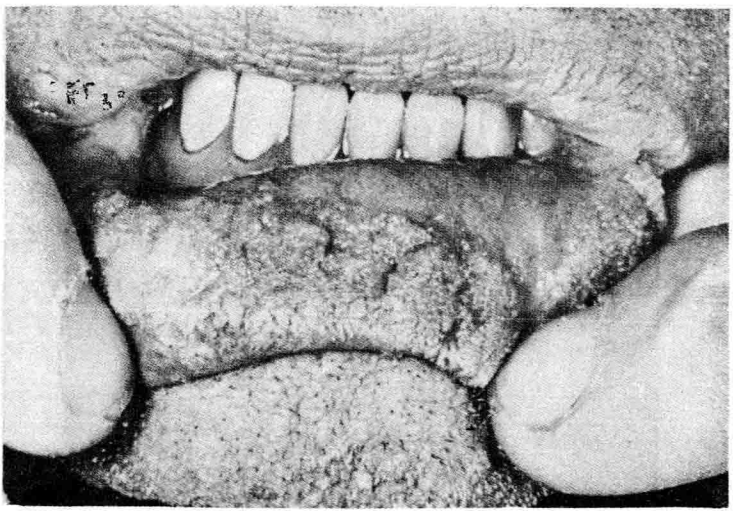

FIG. 1-4. Thickening of labial mucosa and papillomatosis. Pigmentation of oral mucosa is characteristically absent. (*Courtesy of Dr. A. Proppe, Kiel, Germany.*)

cent. Of course, it should be realized that the oral mucosa is seldom thoroughly inspected in the course of a general examination.

Of all oral tissue, the tongue and lips are involved most frequently and to the greatest degree. The dorsum of the tongue, or at times the lateral border, exhibits hypertrophy and elongation of papillae. These give the tongue, marked by deep fissures or furrows, a shaggy or prickly appearance. In addition, one may see papillomatous growths studding its surface. In contrast to the skin, these growths are rarely, if ever, pigmented (1,3–7,16,20,23,25,27–29,35,39–42).

The lips, especially the upper lip, may be markedly enlarged and covered by filiform or papillomatous growths which are especially marked at the angles of the mouth (1–4,12,16,19,22,23,27,28,35,41,42) (Figs. 1-3, 1-4).

The buccal mucosa is usually less severely involved. One generally finds a diffuse unevenness of its surface and a velvety white appearance (Figs. 5,6). Occasionally, single fungiform growths are observed (6,12, 17,19,26,27,39,40). The palate may be similarly affected (1,4,28,35). The gingiva, especially the interdental papillae, may become so much enlarged as almost to cover the teeth, resembling idiopathic fibromatosis. Although the teeth have been noted to loosen and to be shed, the frequency of this phenomenon is yet to be determined (4,6,19,23,27).

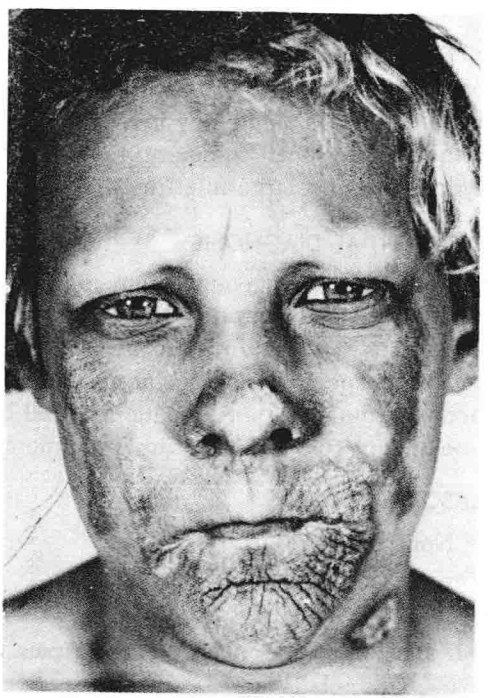

FIG. 1-5. Benign or juvenile *acanthosis nigricans*. Note papillomatous-like lesions circumorally.

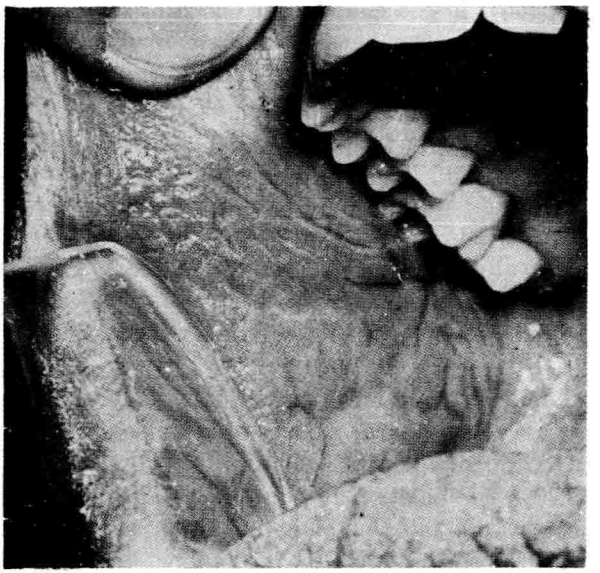

FIG. 1-6. Intraoral changes in patient seen in Fig. 1-5. Note numerous furrows on buccal mucosa. (*Figs.* 1-5 *and* 1-6, *from J. J. Pindborg, and R. J. Gorlin, Acta dermato-venereol.* 42:63, 1962.)

There is insufficient evidence in the literature to suggest the frequency of oral involvement in the benign form of the disease (20,33,43). The vaginal mucous membrane may also be the site of verrucous lesions (37). Readett (personal communication, 1961) indicated that the pharynx, esophagus, and large intestine may be involved as well.

DIFFERENTIAL DIAGNOSIS

Regarding endogenous pigmentation, one should consider Addison's disease, arsenic poisoning, and hemochromatosis, but in none of these conditions is there an associated papillomatosis. Ichthyosis hystrix, bromoderma, pemphigus vegetans, hyalinosis cutis et mucosae, condyloma acuminatum, and hairy tongue must all be ruled out as well. In Negroes, one should rule out dermatosis papulosa nigra.

LABORATORY AIDS

None is known.

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2

Acrocephalosyndactyly

(Apert's Syndrome, Akrokranio-Dysphalangie, Sphenakrokranio-Syndaktylie, Acrodysplasia)

Acrocephalosyndactyly is a rare variant among the craniostenoses, characterized by (*a*) oxycephaly (acrocephaly) and (*b*) syndactyly of hands and feet, often combined with anomalies of various other organs. The syndrome was mentioned as early as 1842 by Baumgärtner (2) and by Wheaton in 1894 (28), though eponymic credit is given to Apert (1) for his presentation of the syndrome in 1906. In 1938, Valentin (23) thoroughly reviewed 83 cases from the literature, and in 1960, Blank (4) established distinct criteria for the syndrome and estimated the incidence to be 1 in 160,000 live births. Because of the high infant mortality, he found the frequency decreased to about 1 in 2,000,000 in the general population. Although Günther (11) found females more often affected than males, Blank (4) reported an equal distribution between the sexes. Over 150 cases have been reported (4).

The majority of cases of acrocephalosyndactyly are sporadic. This, however, does not exclude the possibility of new mutations (6,10). In favor of a transmissible condition are (*a*) the reported cases of a familial incidence (18,26); (*b*) the occurrence of partial signs of the syndrome in certain families* in which some members exhibit the full-blown syndrome (3,15); and (*c*) the simultaneous occurrence, in persons with acrocephalosyndactyly, of anomalies known to be genetically determined, such as cleft palate and oxycephaly. The syndrome seems to be transmitted by an autosomal dominant gene (15). Chromosomal studies have revealed a normal complement without evidence of gross chromo-

* Blank (4) considered these cases to be atypical of acrocephalosyndactyly and to be etiologically unrelated to typical Apert's syndrome.

somal abnormality. An advanced male parental age effect has been suggested (4,10).

Several etiologic hypotheses have been proposed, but none has gained general support. Ghigo and Magrini (9) suggested that the syndrome is the result of virus embryopathy following maternal infection. The damaging effect upon the fetus has been thought to occur before the fifth to sixth week of embryonic life, i.e., at the time when the various bones are separated from one another (21). Waardenburg (25) has adhered to the theory that the deformities are brought about by excessive production of cerebrospinal fluid in embryonic life. In view of the current attention given to children born with defects due to Thalidomide (13), careful scrutiny should be given to the antenatal drug consumption of mothers giving birth to children with acrocephalosyndactyly.

SYSTEMIC MANIFESTATIONS

Face: Patients with acrocephalosyndactyly often have facial asymmetry (Figs. 2-1, 2-2). The middle third of the face appears flat and underde-

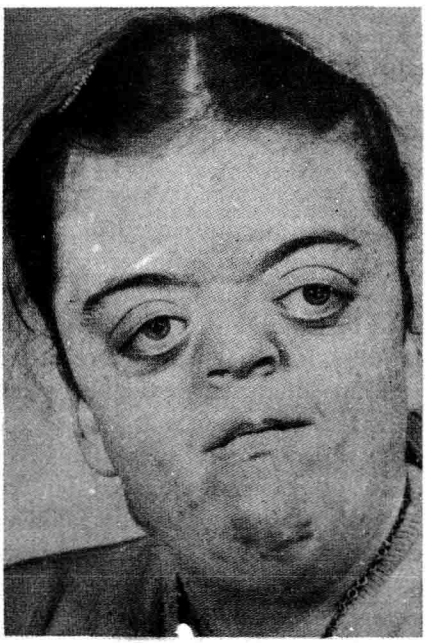


FIG. 2-1.. Acrocephalosyndactyly. Showing typical facies with exophthalmos, small curved nose, and malformation of mouth and lower jaw. (*Courtesy of A. Kahn, Jr., and J. Fulmer, New England J. Med.* 252:379, 1955.)

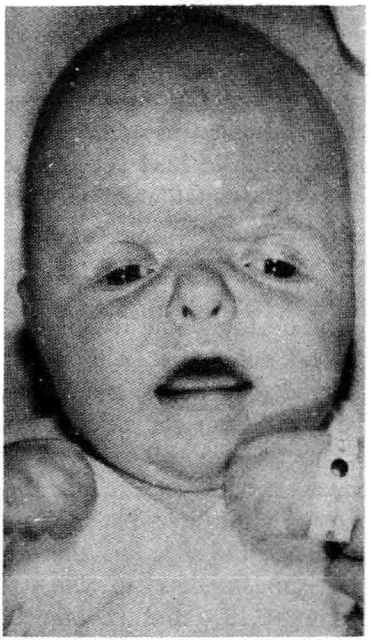
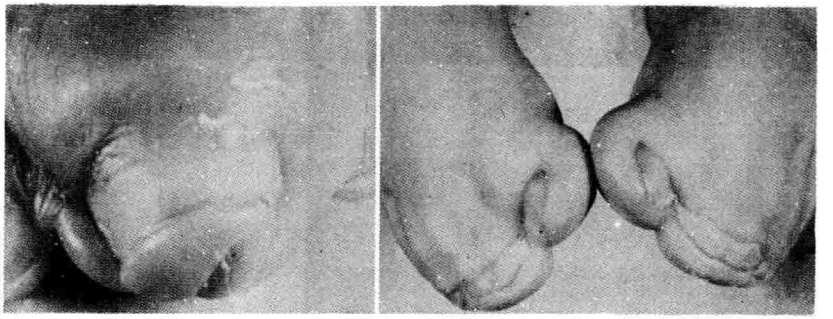


FIG. 2-2. Child with acrocephalosyndactlyly. Note similar facies, frontal bossing, syndactyly.



A B

FIG. 2-3*A* and *B*. Anomalies of extremities, including middigital hand mass and complete fusion of toes.

veloped, producing a relative prognathism. The nose is small and somewhat parrot-shaped. Hypertelorism and strabismus are often noted. The orbits are flattened, and the eyes tend to be proptosed. Commonly, a horizontal groove extends across the forehead just above the supraorbital ridges (21).

Skull: The cranium has a characteristic oxycephalic appearance. It is ovoid and brachycephalic, with a high, prominent, steep forehead. The frontal and temporal areas bulge. The apex of the cranium is located near or anterior to the bregma, the occipital region being flat and in the same vertical plane as the neck. A number of patients possess an open anterior fontanel, which at times continues to an open frontal suture (3). There is irregular early obliteration of cranial sutures. Roentgenographically, fusion of the coronal suture is most often found, alone or together with fusion of the sagittal suture (3). As a result of increased cranial pressure, marked accentuation of digital markings is usually observed.

Syndactylism: As the name of the syndrome implies, there is syndactylism in the patients. This symmetrical defect varies in degree from partial fusion of the skin to a true osseous syndactyly of fingers and toes (Fig. 2-3*A*, *B*). When the fingers are completely fused, there is often a common nail that gives the hand the appearance of a mitten, somewhat like that of Thalidomide children (13). Polydactyly is found occasionally (3,18,19).

Other Findings: The majority of affected patients has an intelligence distinctly below normal (3,4,6,15). Optic nerve involvement produced by elevated intracranial pressure has been reported by Bertelsen (3), and deafness by Grebe (10). A number of skeletal abnormalities has been described as related to acrocephalosyndactyly: aplasia or ankylosis of several joints, especially elbow, shoulder, and hip (1,18,29), ankylosis of

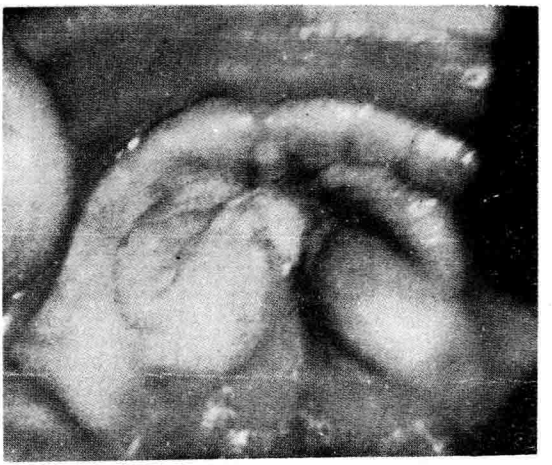


FIG. 2-4. Characteristic palate. Note lateral palatine process swellings.

vertebrae, and spina bifida. Atypical auricular form, encephalopathy (6, 24), heart malformation (20), atresia ani, and numerous miscellaneous associated conditions have been reviewed by Blank (4).

Oral Manifestations: In 12 of 21 cases, Park and Powers (21) found abnormalities in the formation of the hard or soft palate. Most frequently observed is high-arch palate, occasionally with a marked median furrow. Posterior cleft palate, or bifid uvula, is found in at least 25 percent of these patients (1,4,7,29) (Fig. 2-4). When a hypoplastic maxilla is observed (10,27,29,30), it is combined with relative mandibular prognathism and compression of the upper arcade, which becomes V-shaped, leading to an irregular positioning of the teeth. Crowding of the teeth may lead to a marked thickening of the alveolar process (4,8). The pointed arcade may cause protrusion of the middle portion of the upper lip. A few cases with retarded eruption of teeth have also been recorded (11).

Increased salivation has also been observed (22,23), as well as macroglossia (2).

DIFFERENTIAL DIAGNOSIS

It is apparent that acrocephalosyndactyly bears a rather strong resemblance to *craniofacial dysostosis*, and it is not surprising that the two conditions have been observed in the same patient (12). Facial deformity, however, is more marked in craniofacial dysostosis. Some authors (16) have maintained that the condition cannot be called acrocephalosyndactyly if hypoplasia of the intermaxillary bone and prognathism are present.