CASE STUDIES

Cowden’s Disease
A Possible New Symptom Complex with Multiple System Involvement

KENNETH M. LLOYD, II, M.D., and MACEY DENNIS, M.D.

Youngstown, Ohio

In recent years an accelerated interest has been directed toward a better understanding of the rare, familial, developmental diseases. The purpose of this communication is to define an unusual symptom complex which previously has not been described. Because of the multiplicity of findings, and the ill-defined classification for this disease, it shall be referred to as “Cowden’s disease,” the family name of the propositus. The clinical findings include: an adenoid facies; hypoplasia of the mandible and maxilla; a high-arch palate; hypoplasia of the soft palate and uvula; microstomia; papillomatosis of the lips and oral pharynx; scrotal tongue; multiple thyroid adenomas; bilateral virginal hypertrophy of the breasts with advanced fibrocystic disease and early malignant degeneration; pectus excavatum; scoliosis; space-occupying lesions in the liver and bone; abnormalities of the central nervous system; and a history of forme fruste of the syndrome in other members of the family.

CASE REPORT

A 20-year-old female was admitted to the Youngstown Hospital Association on March 14, 1962, because of a lesion on her right breast.

The patient had enjoyed good health until 2 months prior to admission when she developed a small, draining, ulcerative area on the inferior lateral surface of the right breast following minor trauma. This failed to heal in the subsequent months.

The patient had had difficulty with her breasts since her menarche at the age of 12 years, when the breasts had rapidly and progressively enlarged to an abnormal degree with the development of multiple, occasionally tender nodules of varying size. The skin overlying the breasts became increasingly discolored with frequent ulceration and drainage. Healing of these ulcerations was always retarded, but usually complete within a few weeks.

A biopsy of a nodule in the left breast was done at the age of 16, and it was reported as showing fibrocystic disease of the breast. Bilateral simple mastectomy was recommended at the time but was refused. Hormone therapy was of no therapeutic benefit and was discontinued 2 years prior to the present admission.

PAST HISTORY

The patient had had her thymus irradiated at the age of 2. She had had all her teeth extracted at the age of 16 because of advanced decay and malocclusion.

FAMILY HISTORY

The patient’s mother, age 55, has a large goiter and a marked emotional stutter. A sister, who died accidentally at the age of 20, had a high-arched palate, difficulty with articulation, a pectus excavatum, a large thyroid tumor, mild mental retardation, and numerous small firm skin tumors of an unknown nature. Her remaining sibling, a 24-year-old female, appears to be normal with none of the physical characteristics of her sisters.

Two maternal aunts died of carcinoma of the breast. One maternal aunt died in a state mental institution at the age of 35 of post-encephalitic parkinsonism. She was described as having had
**Figure 1. Twenty-year-old patient.**

**Figure 2.** Showing typical adenoid facies, with sharp-beaked nose, microstomia, short mandible, and long narrow head.
progressive mental deterioration, a masked facies, a coarse intention tremor, and incoordination. Four maternal aunts and 5 maternal uncles are alive and show none of the stigmata of the patient.

The patient's father died at age 67 of congestive heart failure secondary to rheumatic heart disease. None of the characteristics of the syndrome could be identified in the paternal relatives.

REVIEW OF SYSTEMS

The patient has been myopic since the age of 10, and wears corrective lenses. Since early childhood, she has had difficulty speaking because of the structural abnormalities of her oral cavity. She has always been a mouth breather. She is a frequent victim of colds with persistent sinusitis and pharyngeal catarrh. For the past 4 years, she has noticed a slowly enlarging mass at the base of her neck. The mass is not painful or bothersome. There has been recent enlargement. Her mentality is below average; an intelligence quotient of 85 was recorded while she was in high school. Coordination for finer movements has always been poor. The patient has had frequent periods of amenorrhea since menarche, and had not menstruated during the 4 months prior to admission.

Physical examination revealed a poorly-developed, well-nourished, asthenic-appearing Caucasian female weighing 120 pounds (Figure 1). The blood pressure was 130/70 mm Hg; pulse, 110/min and regular; temperature, 98.6°F; and respirations were 16/min. The patient demonstrated the typical

Figure 3. Hyperkeratotic papillomata over surface of lips.

Figure 4. Hyperkeratotic papules, similar to those on lips, cover alveolar ridges and palate.
adenoid facies characterized by a sharp-beaked nose, microstomia, a short mandible, and a tall narrow head (Figure 2). The lenses were not dislocated, and the fundi were normal. The nose was narrow with small external nares. The turbinates were thin; the posterior nares were patent. The nasal mucosa was pale and covered with numerous dried crusts and purulent secretions. A 10% hearing deficiency was apparent with the 1,024 frequency tuning fork. There were multiple hyperkeratotic papillomata over the surface of the lips, most marked on the lower lip (Figure 3). The patient was edentulous. Both the maxilla and mandible were narrowed. The alveolar ridges and the palate were covered with hyperkeratotic papules similar to those on the lips (Figure 4). The hard palate was highly arched and shorter than normal. The soft palate and the uvula were hypoplastic. The tonsils and adenoids were not enlarged. The tongue was thickened, narrowed, and deeply furrowed both laterally and longitudinally. The anterior cervical and submaxillary nodes were enlarged. These nodes were soft, non-tender, and freely movable. There was a soft rubbery, movable mass, measuring 6 by 5.5 cm, in the right lower neck anteriorly, which moved on swallowing. There was a smaller 2 by 2 cm nodule of similar consistency just to the left of the larger mass. No bruit was heard over the mass, nor did the mass transmit ultrasound. The thorax was asymmetrical because of a lowering of the right shoulder. Numerous superficial dilated venous channels were present over the anterior chest. A moderate pectus excavatum was present, its depth being accentuated by the large breasts. The breasts were grossly deformed, due to their size, nodular appearance, and hyperpigmentation (Figure 5). The skin overlying the breasts was shiny and atrophic with a reddish-blue, mottled, reticulated discoloration with interpersed hyperpigmentation extending out from the areolae. The nipples were atrophic, and appeared to be eccentrically placed in relation to the areolae. The left nipple was inverted. There was a 1 by 1.5 cm ulcerative area, with a base of granulation tissue on the inferior lateral aspect of the right breast, 3 cm from the chest wall, exuding a seropurulent discharge. No sinus tract was present. The right breast was 20 cm in circumference, the left being slightly larger. Scars of previous ulcers were plentiful. On palpation, both breasts were filled with multiple, moderately tender nodules varying greatly in size. In many areas, the nodules felt confluent. Many of the nodules were fixed to the skin. No dimpling was apparent. There was no fixation to the chest wall. Prominent discrete nodes were present in both axillae, most numerous in the right. The nodes were firm, freely movable, and slightly tender. The lungs were clear to percussion and auscultation. Examination of the heart revealed a persistent sinus tachycardia and a short grade 1/6 systolic murmur at the base and the apex without radiation. No abnormalities were noted on examination of the abdomen. The ex-

Figure 5. The dark circular area to the right of the sternum is an artifact produced by a vacuum cup of an electrocardiograph machine.

ternal genitalia and hair distribution were those of an adult female. Speculum examination of the vagina revealed a profuse, watery, bubbly, white discharge. The vaginal mucosa was inflamed. Bi-manual examination revealed a long cervix and a small retroverted infantile uterus. Both ovaries were palpated and found not to be enlarged or cystic. The patient had a slight kyphoscoliosis. The head was carried forward. Her total height was 68 inches, and her “wing span” was 67.5 inches. The right leg was 3/4 inch shorter than the left. Hyperflexibility of the joints was not present. Numerous verrucae simplex were present over the dorsa of both hands. A linear area of hyperpigmentation was present over the vertebral spines from T6 to L2, resembling traumatic hyperpigmentation. The cranial nerves were intact, except for weakness with drifting of the left eye on left lateral gaze, and some loss of conjugate eye movements. Deep tendon reflexes were normal, and no pathological reflexes were demonstrated. The muscle strength was normal. Sensory examination was normal. Coordination was poor. A coarse intention tremor was apparent during all fine movements. The finger to nose and heel to toe tests were performed poorly. A positive Romberg test was present. Bilateral idiomotor apraxia was apparent. Adiadochokinesia was absent. The sensorium was clear, and the patient was well oriented.
LABORATORY STUDIES

Blood count on admission revealed RBC, 5.18 million mm²; hematocrit reading of 40.5%; hemoglobin of 12.8 g/100 ml; and WBC, 5900/mm³, with a normal differential. The urine was yellow, with a specific gravity of 1.010, and it contained a trace of protein. Three to 5 RBC/high power field, 8 to 12 WBC/high power field, and many trichomonads were seen on microscopic examination of the urine. The serology was nonreactive. The protein bound iodine was 12 μg/100 ml. Normal results were obtained in the following tests: total serum proteins; albumin/globulin ratio; serum protein electrophoresis; blood urea nitrogen; fasting blood sugar; serum calcium, phosphorous; electrolytes; serum glutamic oxaloacetic transaminase; lactate dehydrogenase; alkaline phosphatase; a bone marrow; serum cholesterol; uric acid; creatinine; a phenolsulfonphthalein test, a Bromsulphalein test; serum amylase; serum lipase; and urine cultures. Staphylococcus aureus, coagulase positive, was cultured from the ulcerative area of the right breast. Papanicolaou smears showed a high estrogen effect. Urinary gonadotrophin and estrogen determinations were within normal limits. Urinary 17-ketosteroids were 5.3 mg/24 hr, with a normal of 5 to 15 mg/24 hr. The urinary 17-hydroxysteroids were 5 mg/24 hr, the normal being 2.8 to 4.7 mg/24 hr. The sex chromatin mass was present in 21% of the cells on buccal mucosal smear.

Roentgenograms of the skull, the sinuses, the spine, the long bones, the chest, and a flat film of the abdomen demonstrated the pectus excavatum, marked calcification of costal cartilages, and the presence of several small confluent areas of decreased density in the distal and lateral portion of the head of the right femur. An upper gastrointestinal series, a barium enema, a gall bladder series, and an intravenous pyelogram were normal.

The electrocardiograms showed a persistent sinus tachycardia with non-specific ST segment and T wave changes.

Respiratory function studies showed a one-second vital capacity of 1.2 liters, a total vital capacity of 2.4 liters (64% of normal), and a maximal expiratory flow rate of 96 liters/min.

Radioactive 131I function studies, with automatic scanning of the thyroid gland, were done. A dose of 50 μc was used. The 2-hour uptake was 27.78%; the 6-hour uptake was 34.62%; and the 32-hour uptake was 24%. The conversion ratio 131I protein bound iodine was 53% (24 hr). Manual scanning of the thyroid showed a high initial concentration within the palpable nodules, with a later loss of radioactivity at the periphery of the nodules indicating multiple hyperactive nodules with evidence of degeneration.

Scintillation scanning of the liver performed after the intravenous injection of 200 μc of 131I tagged rose bengal identified multiple, large, well-defined areas of absent isotope concentration, suggesting the presence of tissue other than functioning liver tissue.

An electroencephalogram was performed using amobarbital, 3/4 gr, one-half hour before the test. Much of the dysrhythmic activity was attributed to the normal sleep pattern; however, persistent shifting left temporal lobe discharges of a non-specific nature were recorded.

Biopsies were obtained from the lips, tongue, and alveolar ridge for histological examination. All 3 of the specimens showed epithelial hyperplasia, papillomatosis, and focal areas of parakeratosis and acanthosis. Moderate prolongation of the rete ridges was apparent. The sections differed in the degree of dermal infiltration by chronic inflammatory cells, the infiltration being more abundant in the sections of the tongue than in the other 2 areas. The fibrous tissue and capillary vascularity of the dermis were increased in the sections of the alveolar ridge.

Three transcutaneous needle biopsies of the liver were done, to obtain tissue from the areas outlined by the scintillation scanning of the liver. All specimens, however, showed normal hepatic histology.

Histological appearance of a specimen obtained by needle biopsy of the thyroid mass was that of a fetal adenoma.

During the patient's hospitalization a bilateral modified simple mastectomy was performed. The right breast weighed 1 kg and the left weighed 0.8 kg. Sectioning of the breasts showed multiple unilocular cysts. The cysts varied in size from 3 mm to 3 cm in diameter, and were filled with a viscous yellow to dark brown fluid. Firm bands of fibrous tissue separated the cystic spaces. Histologically, the breasts showed a marked intraductal epithelial papillomatosis and a florid adenosis. The connective tissue stroma surrounding the dilated ductules had a densely fibrous hyalinized appearance. Chronic inflammatory cells were scattered throughout the sections. In one section from the right breast the epithelial overgrowth was indistinguishable from carcinoma. No areas of invasion into the surrounding tissue could be found. Fifteen lymph nodes from the right axilla showed no evidence of metastases.

DISCUSSION

Whether this case represents a new familial disease, an aberrant gene giving rise to multiple congenital defects, or a conglomeration of unrelated single disease entities has not been established. Certainly, from a statistical point of view, the probability of so many isolated abnormalities occurring in the same patient makes coincidence improbable.

All of the constituents of this symptom complex, excluding the papillomatosis of the lip, have been described as isolated findings with varying degrees of frequency, throughout the English literature.
The high-arched palate occurs frequently, tends to run in families with a predisposition for cleft lips and palates, and is a constituent of a well-known familial syndrome, Marfan's syndrome (1, 2).

The adenoid facies or bird-like facies, with the associated hypoplasia of the mandible and maxilla, is a secondary developmental abnormality which may occur when persistent nasal obstruction develops in infancy, regardless of the cause of the obstruction.

Scrotal or fissured tongue has been recognized for many years. Until recently, it was accepted as a familial abnormality (3), but this thesis has been questioned by Halperin and his colleagues (4), who believed the fissured appearance to be secondary to long-standing irritation and chronic inflammation. It is usually a benign asymptomatic finding not associated with other abnormalities, except in the Melkerson-Rosenthal syndrome (5).

The papillomatosis of the palate and alveolar ridge appears, both clinically and histologically to be similar to that of the lip. Similar lesions have been described in journals of oral surgery, occurring after long-standing irritation from ill-fitting dentures, a not unlikely possibility in our case (6, 7).

Thyroid adenomas are common in the locale of the patient's home, and careful consideration is required to differentiate them from thyroid carcinoma. The adenoma in this case is of interest for several reasons: first, the young age of the patient at the onset of the nodule; second, the history of similar lesions in the patient's mother and sibling; and last, the recent correlation between thyroid carcinoma in adolescents and thymic irradiation between the fourth and sixteenth months of life (8, 9).

Virginal breast hypertrophy of adolescent females was infrequently encountered in the literature. Approximately 50 cases had been described to 1955 (10). No familial tendency was noted. All patients presented were physically normal except for the breast disease, other than a 14-year-old girl, who also had mental retardation and spastic diplegia (11), and one adolescent girl with macrogingivae and hypertrichosis (12). The pathological material obtained from these cases was greater than in our case, the average weight of the breasts being 15 to 25 pounds. Only 2 of the above patients showed clinical and histological evidence of malignancy. However, the occurrence of carcinoma of the breast in women with fibrocystic disease is not uncommon (13).

Pectus excavatum has been reported since 1596, and is known to have a familial tendency (14). While associated with musculoskeletal deformities, such as kyphosis and scoliosis, it is not regularly associated with any particular congenital or familial disease complex other than Marfan's syndrome.

The space-occupying lesions in the liver are of unknown pathology. Most likely, these nonfunctioning areas demonstrated by the scintillation scanning of the liver are multiple, nonparasitic cysts. They are commonly associated with polycystic disease of the kidneys, and in 8 per cent of reported cases are familial (15). The failure to obtain tissue for diagnosis by transcutaneous biopsy was not unexpected. These cysts, when asymptomatic, are usually found at autopsy, or incidentally at laparotomy (16–18).

The bone cysts are probably of no pathological significance, although solid tumors cannot be excluded. A significant percentage of the population would undoubtedly demonstrate similar lesions, if total skeletal radiographs were taken routinely.

The nature of the lesion producing the patient's neurological findings has not been demonstrated, and any discussion of the possibilities would be speculative. The diversity of the neurological findings, however, suggests the presence of a diffuse disease process rather than a focal one.

At the present time, it appears safe to say only that this case represents an interesting association of clinical findings which may be genetically linked. Until more cases of a similar nature are described with a careful consideration of genetics, the classification of this symptom complex remains an individual matter.

**Summary**

A 20-year-old female had multiple developmental defects including: an adenoid facies; a scrotal tongue; hypoplasia of the mandible and maxilla; a high-arched palate; papillomatosis of the lips and oral pharynx; multiple thyroid
adenomas; pectus excavatum; bilateral virginal hypertrophy of the breasts with extensive fibrocystic disease and early malignant degeneration; scoliosis; space-occupying lesions in the liver and bone; and a history of forme fruste of this symptom complex in other members of the family.

ADDITIONAL INFORMATION

Additional information has been obtained since this paper was submitted for publication.

A lumbar puncture was done. Manometrics and other laboratory studies of the spinal fluid were normal.

A subtotal thyroidectomy was performed on the patient 3 months after the bilateral mastectomy. The specimen consisted of several large adenomas which, on microscopic examination, revealed a marked papillomatosis and adenosis with areas indistinguishable from carcinoma. These proliferative changes were similar to those found in the microscopic sections of the breast tissue.

Studies of the patient’s chromosome pattern were done and failed to reveal any abnormalities.

A fourth transcutaneous liver biopsy was done. On microscopic examination of the sections, well-circumscribed nodules of epithelioid cells infiltrated with lymphocytes were found. No giant cells or areas of necrosis were present. These multiple granulomata were non-specific in character, and no definite etiology was identified.

Scintillation scanning of the liver was repeated, using a different scanning device. Two hundred µc of 131I tagged rose bengal were injected intravenously. The space-occupying lesions were not identified. This would appear to negate the original findings. Peritoneoscopy, which might have resolved this problem, was suggested but was refused by the patient.

ACKNOWLEDGMENT

The chromosomal patterns were done by Margery W. Shaw, M.D., Department of Human Genetics, University of Michigan Medical School, Ann Arbor, Michigan.

SUMMARIO IN INTERLINGUA

Es presentate le caso de un feminina de 20 annos de etate, con multiple defectos disveloppamental incluse facie adenoide, lingua scrotal, hypoplasia mandibularis e maxillaris, un palato alti-arcate, papillomatosis del labios e pharynge oral, multiple adenomas thyroidic, pectore excavate, bilateral hypertrophia virginal del mammis con extense morbo fibrocystic e precoce degeneration maligne, scoliosis, lesiones recrudescente in hepate e osso, e le antecedentes de “forme fruste” del mesma complexo de symptomas in altere membros del familia.

REFERENCES
