Cowden's Disease
- A Report on the First Case in Korea and Literature Review -

Cowden's disease, or multiple hamartoma syndrome, is an uncommon condition with characteristic mucocutaneous lesions associated with abnormalities of the breast, thyroid, and gastrointestinal tract. We describe a 32-year-old man with oral mucosal papillomatosis and plantar hyperkeratosis as a definite case of Cowden's disease according to the criteria proposed by Salem and Steck. The patient also had a thyroid mass and numerous gastrointestinal polyps endoscopically. Histologically the polyps were hamartomatous or hyperplastic polyps. The oral papillary lesions were fibroepithelial polyps and the thyroid mass was a follicular adenoma. We review the literature on this entity and summarize the pertinent findings. To the best of our knowledge, this is the first documented case of Cowden's disease in a Korean.
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Key Words : *Hamartoma syndrome, Multiple; Polyps*

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INTRODUCTION

Cowden's disease is usually inherited as an autosomal dominant condition and is characterized by multiple hamartomatous malformations of the endodermal, mesodermal, and ectodermal layers. Several sporadic cases have also been reported. The most consistent findings are the mucocutaneous lesions that include facial trichilemmomas, oral papillomas, and acral and palmoplantar keratoses. The internal abnormalities associated with this condition involve the breast, thyroid gland, and gastrointestinal system. We recently experienced a case of a 32-year-old man with Cowden's disease with multiple cutaneous facial papules, oral mucosal papillomatosis, plantar hyperkeratosis, a thyroid adenoma and gastrointestinal polyposis. To the best of our knowledge Cowden's disease has not been reported previously in Korea. We report this rare condition along with a brief review of the literature.

CASE REPORT

A 32-year-old male patient was admitted to the Department of Family Medicine at our hospital for the evaluation and treatment of an enlarged neck mass and hoarseness of 6-years duration. The patient had also experienced indigestion with abdominal discomfort on a few occasions for about a year, but had not received any treatment. His abdominal discomfort had become more severe since 1 week prior to admission. His medical history was otherwise unremarkable. None of his family members had cutaneous facial papules, oral mucosal papillomatosis, acral or palmoplantar keratoses, dermatosis, gastrointestinal polyposis or thyroid disease.

On physical examination, multiple mucocutaneous lesions were observed. The facial skin showed multiple, small, skin-colored, smooth, hyperkeratotic papules (Fig. 1). Oral examination showed several 1 to 2 mm, shallow oral ulcerative lesions and bilateral tonsillar enlargement (Fig. 2) and a papillomatous lesion on the tip of the tongue (Fig. 3). On the tongue base, a 1 cm polyp was observed with multiple papillomatous lesions. On the

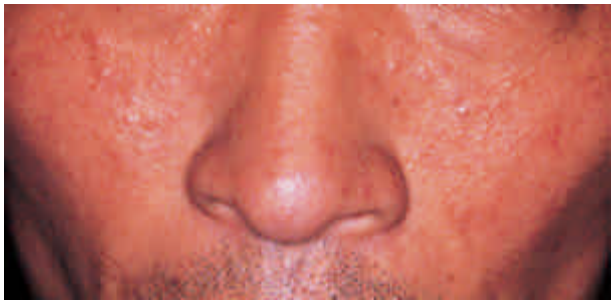

Fig. 1. There are multiple papular lesions on the face.

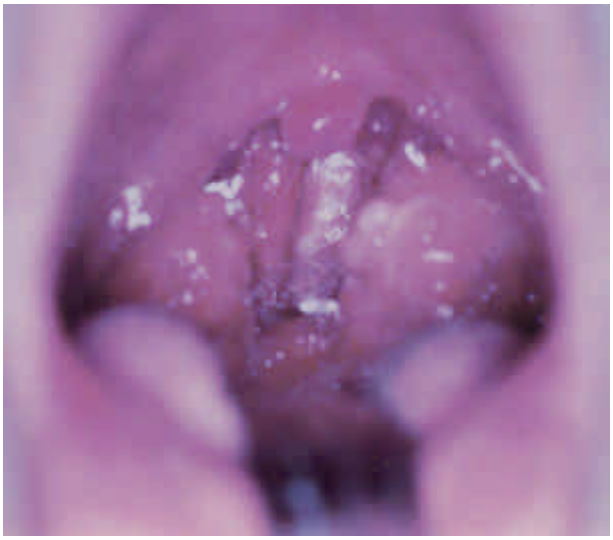

Fig. 2. There is bilateral tonsillar enlargement with multiple papillomatous lesions.

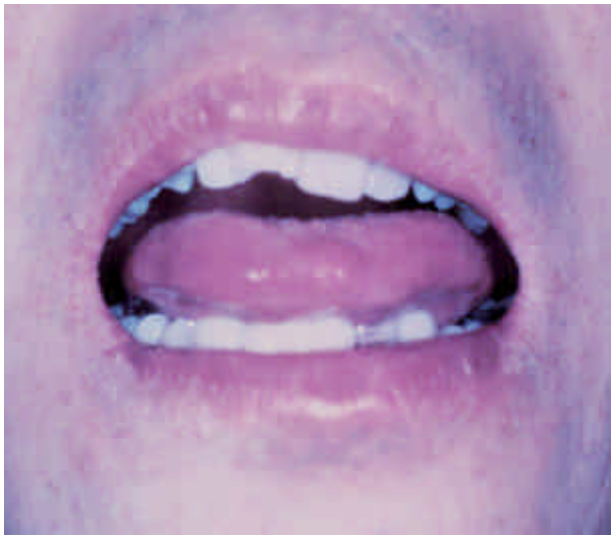

Fig. 3. There is a papillomatous lesion on the tongue tip.

extremities, plantar hyperkeratosis was noted (Fig. 4) with nail dystrophy. A 6×8 cm sized firm, movable, and nontender mass lesion with a smooth surface was found on the left side of his neck.

On cardiac auscultation a grade I/IV pansystolic murmur was heard at the apex. On palpation of the abdomen, there was direct tenderness on the epigastrium but no organomegaly was found. The rectal examination was unremarkable.

Laboratory findings showed mild elevation of liver enzymes, SGOT 41 IU/L, SGPT 59 IU/L with HBsAg (+), anti-HBc (+), anti-HBs (+), HBeAg (+), and anti-HBe (−). Thyroid function tests showed T3 159 ng/dl, fT4 1.0 ng/dl, TSH 0.2 μIU/ml. Serologic tests for thyroid auto-antibodies revealed anti-thyroglobulin antibody $1:10^2$ (+), anti-microsomal antibody (−). The CEA level was within normal limits (1.3 μg/L). The chromosomal study of the patient was normal (46, XY).

A computed tomogram of the neck showed a 1 cm sized polypoid nodular mass on the right palatine tonsil,

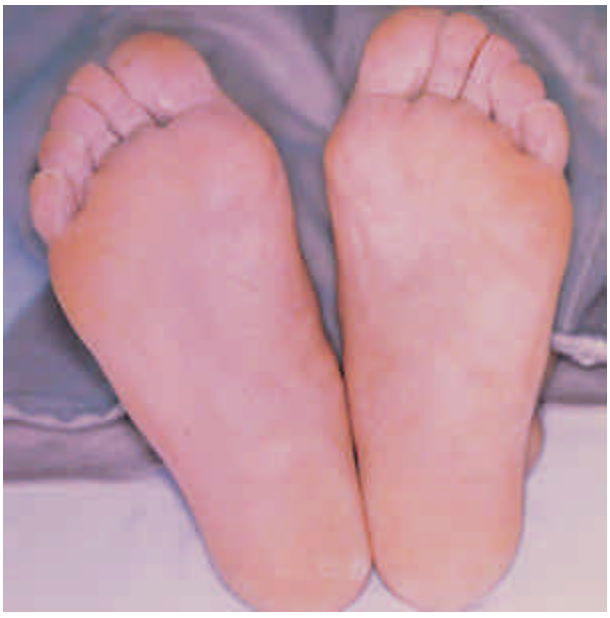

Fig. 4. There is plantar hyperkeratosis.

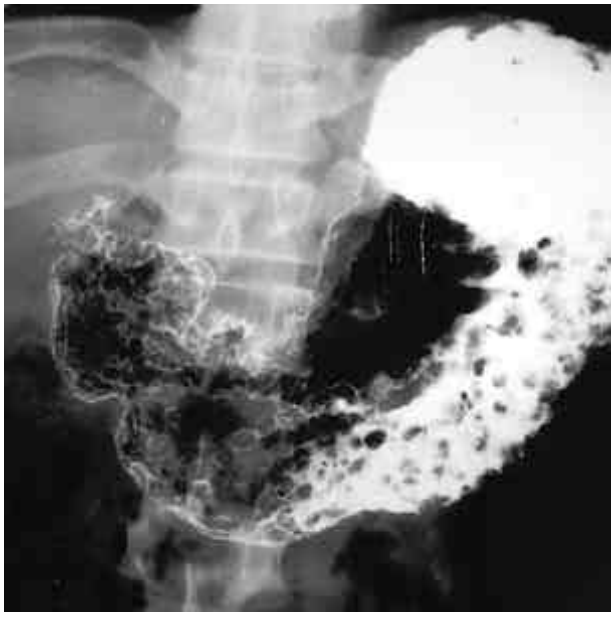

Fig. 5. Double-contrast upper gastrointestinal series shows numerous small polyps in the entire stomach.

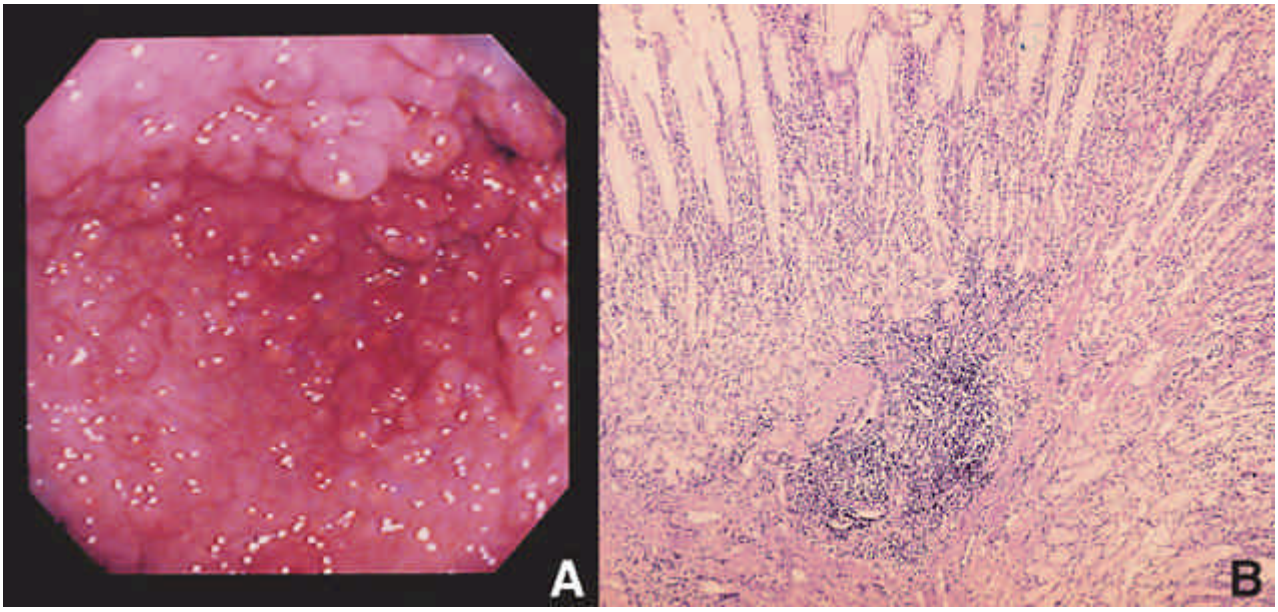

Fig. 6. A: Endoscopy of the stomach shows numerous 5-15 mm sized polyps. **B:** Histopathology of a gastric polyp shows proliferation of pyloric glands and stomach muscles, consistent with hamartomatous polyp.

multiple small sized nodular densities around both palatine tonsils and there was also a 5×6×5 cm sized bulky mass in the left thyroid gland. Ultrasonography of the patient's neck showed a 7×4×6 cm sized homogenous isoechoic mass in the left thyroid gland. On a thyroid iodine uptake scan there was a huge cold nodule in the left thyroid gland and radioactive iodine uptake was decreased.

The chest X-ray showed no active parenchymal lung lesion or mass. The echocardiogram showed ruptured chordae of the anterior mitral leaflet and mitral and aortic insufficiency.

A double-contrast upper gastrointestinal series showed numerous small polyps up to 4 mm in size distributed throughout the stomach (Fig. 5). Esophagogastroduodenoscopy showed multiple polyposis in the entire lumen of the stomach and duodenum (Fig. 6A). Biopsy of the gastric lesion and polypectomy revealed hamartomatous polyp with *Helicobacter* gastritis (Fig. 6B). The small bowel series showed multiple polyposis throughout the entire small bowel. A double-contrast barium enema showed multiple polyposis in the ileocecal and rectosigmoid colons sparing the ascending, transverse and descending colons. Colonoscopy revealed multiple polyps affecting the area within 45 cm from the anal verge (Fig. 7) and a colonoscopic polypectomy was also performed. The colon polyp was tubular adenoma.

Since the patient had a huge neck mass and hoarseness, an operation was performed on the 16th hospital day. Left hemithyroidectomy with isthmectomy and tonsillectomy (Fig. 8A), and tongue base polyp excision were performed. The thyroid mass was a follicular adenoma with oxyphilic change (Fig. 8B). The pathology of the resected tonsil was chronic follicular tonsillitis with epithelial hyperplasia and dense fibrous tissue deposition in the subepithelial layer, and the tongue base polyp was a fibroepithelial polyp (Fig. 9).

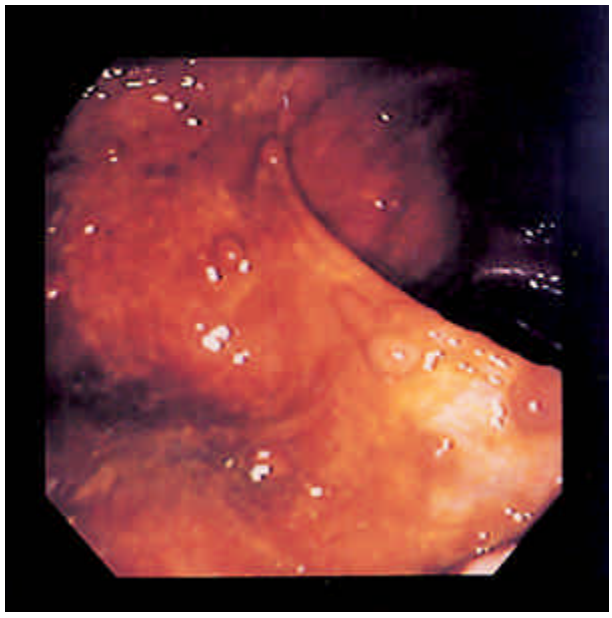

Fig. 7. Colonoscopy shows several small polyps.

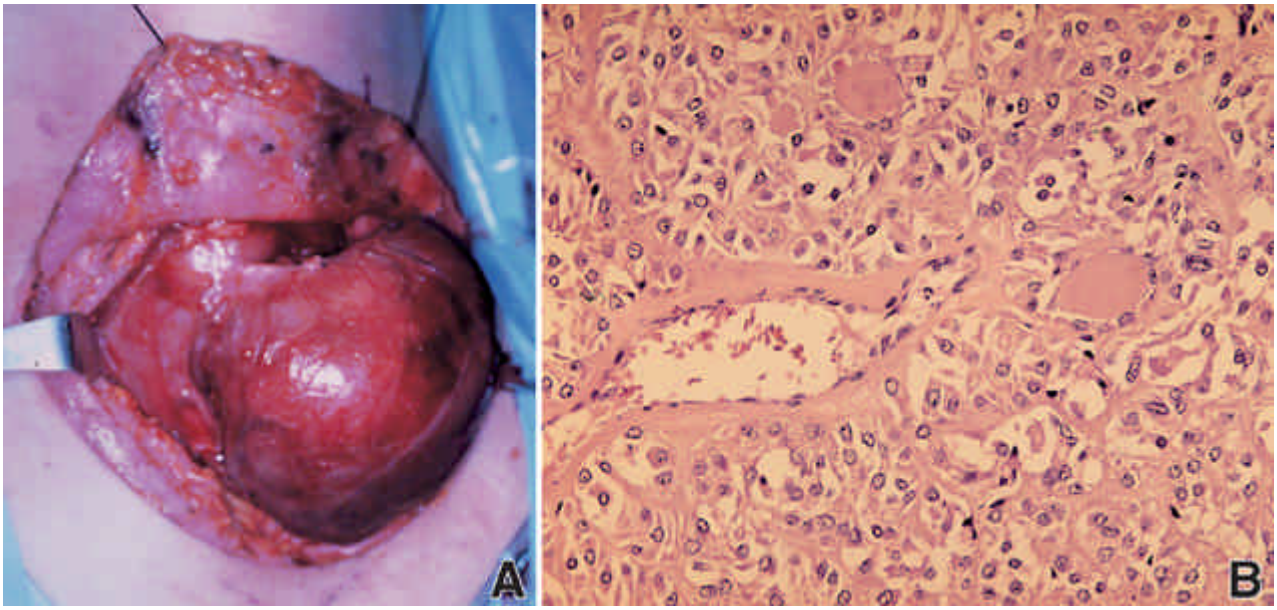

Fig. 8. A : Left hemithyroidectomy with isthmectomy and tonsillectomy is shown. **B :** Histopathology of a thyroid mass shows follicular adenoma with oxyphilic change.

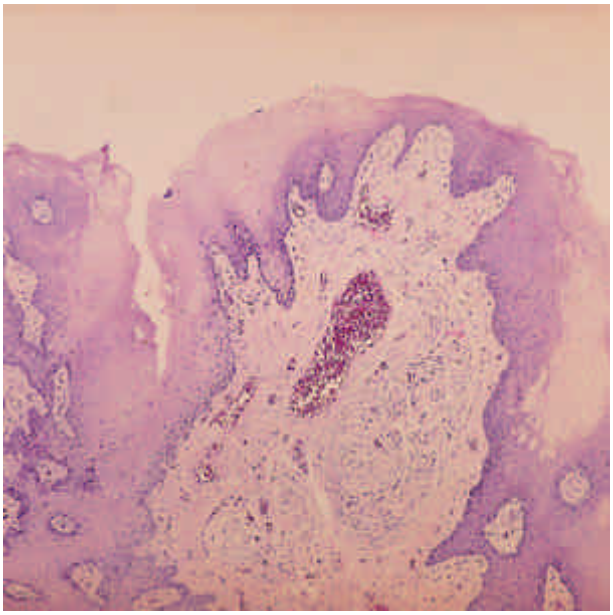

Fig. 9. Histopathology of the tongue base fibroepithelial polyp shows hamartomatous growth of connective tissue and nerve bundles.

DISCUSSION

Cowden's disease is characterized by multiple hamartomas of triploblastic origin, a high incidence of malignant tumors of the breast and/or thyroid gland, and an autosomal dominant pattern of inheritance. Cowden's disease was first described by Lloyd and Dennis in 1963, Cowden being the surname of the first family diagnosed as having this condition (1). In 1972, Wearry et al. reported five additional cases and suggested the name, "multiple hamartoma syndrome" as their patients presented with hamartoma of all three germ layers (2). In 1976, Gorlin et al. named it as "multiple hamartoma and neoplasia syndrome" (3). Since then, approximately 110 additional cases have been reported in the associated literature. The frequency of reports is increasing as knowledge of the disease spreads.

Cowden's disease mainly affects whites (96%) and is more common in women (60%) although the reason is unclear. The age of onset ranges from 4 to 75 years (average age, 39 years) (4, 5). The mucocutaneous lesions are present in almost 100% of cases (6, 7); breast lesions in 76% of cases, with carcinoma of the breast occurring in 36% of female cases (8); and thyroid disease in 67% of patients (9).

The diagnostic criteria for Cowden's disease were proposed by Salem and Steck (10), dividing the diagnostic features into major criteria, minor criteria, and family history (Table 1). Major criteria were defined as cutaneous facial papules and oral mucosal papillomatosis, and minor criteria were defined as acral and palmoplantar keratoses. Diagnosis was to be considered definite in the presence of two major criteria, one major and one minor criteria, one major and a positive family history, or two minor criteria and a positive family history (5, 10, 11). Our patient fulfilled these definite criteria of Cowden's

Table 1. Diagnostic Criteria for Cowden's Disease*

1. Major clinical criteria	
a. Cutaneous facial papules	
b. Oral mucosal papillomatosis	
2. Minor clinical criteria	
a. Acral keratoses	
b. Palmoplantar keratoses	
3. Family history of Cowden's disease	
Definite diagnosis :	1a + 1b
	(1a or 1b) + (2a or 2b)
	(1a or 1b) + 3
	2a + 2b + 3
Probable diagnosis :	1a or 1b
	(2a or 2b) + 3
Possible diagnosis :	2a and/or 2b

* Proposed by Salem and Steck

disease with two major criteria, multiple facial papules and oral mucosal papillomatosis, and one minor criteria, palmoplantar keratoses, with additional involvement in his gastrointestinal polyposis and thyroid adenoma.

The exact nature of the mucocutaneous lesions of Cowden's disease has not been determined (7). The mucocutaneous lesion described is a papule that usually measures 1 to 4 mm in diameter, either smooth or keratotic, and has a predilection for the face and distal extremities, including the palms and soles. The presenting symptoms are mainly facial trichilemmomas, acral keratoses, oral papilloma and palmoplantar keratoses (7, 12-14). Steffen et al. (1993) interpreted the clinical and histopathological features of the mucocutaneous lesions to be verruca (7).

In 67% of cases, the thyroid is affected. Although the lesions are usually benign in nature, such as goiter and adenoma, three cases of follicular adenocarcinoma have been reported (4, 8, 15). Other lesions include fetal adenoma, oncocytoma, thyroid hypofunction or hyperfunction, thyroiditis, and thyroglossal duct cyst (4). Our patient had follicular adenoma.

Gastrointestinal polyp accompanied in 71% of cases, lesions being anywhere in the gastrointestinal tract (16). The pathologic spectrum of the gastrointestinal polyps reported in Cowden's disease includes hamartomatous, juvenile, lipomatous, lymphomatous, inflammatory, hyperplastic, and occasionally adenomatous (17, 18). A few isolated cases reported colonic carcinoma, but the association with Cowden's disease is doubtful (16-21). Differential diagnosis of gastrointestinal polyposis of Cowden's disease should include familial polyposis, Gardner's syndrome, Peutz-Jeghers syndrome, Turcot's syndrome, Cronkite-Canada syndrome, and multiple adenomatous polyps. Other gastrointestinal lesions may also be encountered, such as pararectal abscess, gastric ulcer, cholecystitis, and hepatic hamartoma (19). Our patient showed multiple hamartomatous polyps in the entire stomach, duodenum, small bowels and ileocecal and rectosigmoid colons.

Abnormalities of the genitourinary tract have been reported in 55% of women with Cowden's disease (4). Skeletal abnormalities are found in one third of cases, usually with adenoid face and a high arched palate (4, 10), but no genitourinary or skeletal abnormalities were found in our patient.

A miscellaneous group of conditions include the involvement of the eye (22, 23), the nervous system, the respiratory system (24), and the cardiovascular system (4, 6, 15). The nervous system lesions include neuroma of cutaneous nerve, neurofibroma, meningiomas, and hearing loss (25, 26). Recently, many reports have implicated the possible association between Cowden's disease and Lhermitte-Duclos disease, which is pathologically characterized by global hypertrophy of the cerebellum, coarse gyri and the typical "inverted cortex" pattern (27). Our patient underwent the brain CT scan, showing no global hypertrophy of the cerebellum and meningioma. The cardiovascular abnormalities include hypertension, atrial septal defect, mitral valve prolapse, and aortic and mitral valve insufficiency. Our patient showed ruptured chordae of the anterior mitral leaflet, and mitral and aortic insufficiency on echocardiography. Our patient showed neither eye nor respiratory involvement.

The cause of Cowden's disease is not known. It is a familial hereditary, autosomal dominant condition with incomplete penetrance, positive family histories being present in only half of the cases that have been reported so far (19). Many genetic studies have been done to elucidate the cause of this syndrome, including chromosomal analysis, DNA repair studies, histocompatibility antigen typing, immunoglobulin allotyping, and genes and oncogenes without success (4, 5). Chromosome studies have all reported normal findings in patients with Cowden's disease, the sole exception being one patient who had a pericentric inversion of chromosome 9 [46, XX, inv (9) (p11 q13)] (5). The chromosomal study of our patient showed normal findings.

Cowden's disease is a multisystemic disorder having a significant association with the development of benign and malignant tumors of various organ systems. Because of its potentially serious associations with internal malignancy, early and accurate diagnosis is essential. Our patient has shown no internal malignancy so far, but patients with this disease should be carefully evaluated and closely followed.

REFERENCES

1. Lloyd KM, Dennis M. *Cowden's disease. A possible new symptom complex with multiple system involvement. Ann Intern Med 1963 ; 58 : 136-42.*
2. Weary PE, Gorlin RJ, Gentry WC, Comer JE, Greer KE. *Multiple hamartoma syndrome (Cowden's disease). Arch Dermatol 1972 ; 6 : 682-90.*
3. Gorlin RJ, Pindborg J, Cohen MJr, eds. *Syndromes of the Head & Neck, ed. 2, New York. McGraw-Hill 1976 ; 510-2.*
4. Starink TM. *Cowden's disease. Analysis of fourteen new cases. J Am Acad Dermatol 1984 ; 11 : 1127-41.*
5. Williard W, Borgen P, Bol R, Tiwari R, Osborne M. *Cowden's disease : a case report with analyses at the molecular level. Cancer 1992 ; 69 : 2969-74.*
6. Shapiro SD, Lambert WC, Schwartz RA. *Cowden's disease. A marker for malignancy. Int J Dermatol 1988 ; 27 : 232-7.*
7. Steffen C, Milligan M, Duboise J. *A family with lesions on the face, hands, and buccal mucosa. Cowden's disease. Arch Dermatol 1993 ; 129 : 1505-8.*
8. Burnett JW, Goldner R, Calton GJ. *Cowden's disease. Report of two additional cases. Br J Dermatol 1975 ; 93 : 329-36.*
9. Mallory SB, Stough DB. *Genodermatoses with malignant potential. Dermatol Clin 1987 ; 5 : 221-30.*
10. Salem OS, Steck WD. *Cowden's disease (multiple hamartoma syndrome). J Am Acad Dermatol 1983 ; 8 : 686-96.*
11. Barax CN, Lebwohl M, Phelps RG. *Multiple hamartoma syndrome. J Am Acad Dermatol 1987 ; 17 : 342-6.*
12. Velez-Torres R, Popham T, Redinger R, Callen JP. *Facial papules and nodules, thyroid goiter, and acral keratoses. Arch Dermatol 1987 ; 123 : 1558-9.*
13. Devlin MF, Barrie R, Ward-Booth RP. *Cowden's disease : A rare but important manifestation of oral papillomatosis. Br J Oral Maxillofacial Surg 1992 ; 30 : 335-6.*
14. Requuena L, Gutierrez J, Sanchez YE. *Multiple sclerotic fibromas of the skin. A cutaneous marker of Cowden's disease. J Cutan Pathol 1992 ; 19 : 346-51.*
15. Starink TM, Van Der Veen JPW, Arwert F. *The Cowden's syndrome : A clinical and genetic study in 21 patients. Clin Genet 1986 ; 29 : 222-33.*
16. Taylor AJ, Dodds WJ, Stewart ET. *Alimentary tract lesions in Cowden's disease. Br J Radiol 1989 ; 62 : 890-2.*
17. Hizawa K, Iida M, Matsumoto T, Kohrogi N, Suekane H, Yao T, Fujishima M. *Gastrointestinal manifestations of Cowden's disease. Report of four cases. J Clin Gastroenterol 1994 ; 18 : 13-8.*
18. Marra G, Armelao F, Vecchio FM, Percesepe A, Anti M. *Cowden's disease with extensive gastrointestinal polyposis. J Clin Gastroenterol 1994 ; 18 : 42-7.*
19. Chen YM , Ott DJ, Wu WC, Gelfand DW. *Cowden's disease. A case report and literature review. Gastroint Radiol 1987 ; 12 : 325-9.*
20. Chilovi F, Zancanella L, Perino F, Wallnoefer W, Vigl EE, Colombetti V, Dobrilla G. *Codwen's disease with gastrointestinal polyposis. Gastroint Endoscopy 1990 ; 36 : 323-4.*
21. Gardner DJ. *Cowden's disease (multiple hamartoma syndrome). Semin Roentgenol 1990 ; 25 : 223-4.*
22. Bardenstein DS, McLean IW, Nerney J, Boatwright RS. *Cowden's disease. Ophthalmology 1988 ; 95 : 1038-41.*
23. Yang JH, Cheng HM, Wang LR, Chu KC. *Cowden's disease. Report of the first case in a Chinese. J Dermatol 1994 ; 21 : 415-20.*
24. Sasaki M, Hakozaki H, Ishihara T. *Cowden's disease with pulmonary hamartoma. Intern Med 1993 ; 32 : 39-41.*
25. Rimbau J, Isamat F. *Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease) and its relation to the multiple hamartoma syndrome (Cowden's disease). J Neuro-Oncol 1994 ; 18 : 191-7.*
26. Vital A, Vital C, Martin-Negrier ML, McGrogan G, Bioulac P, Trojani M, Loiseau H, Rougier A. *Lhermitte Duclos type cerebellum hamartoma and Cowden's disease. Clin Neuropathol 1994 ; 13 : 229-31.*
27. Vinchon M, Blond S, Lejeune JP, Krivosik I, Fossati P, Assaker R, Christiaens JL. *Association of Lhermitte-Duclos and Cowden disease : report of a new case and review of the literature. J Neurol Neurosurg Psychiat 1994 ; 57 : 699-704.*