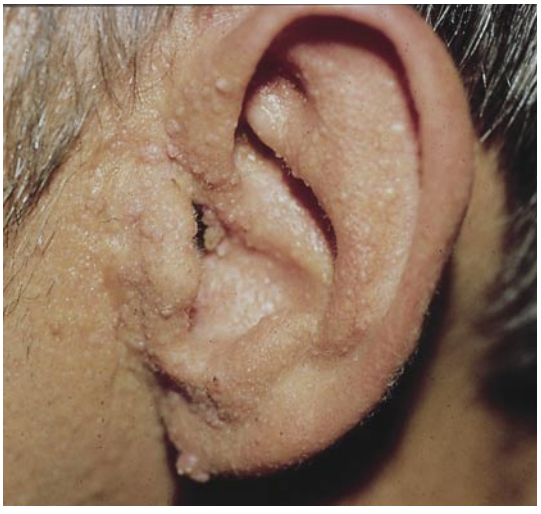
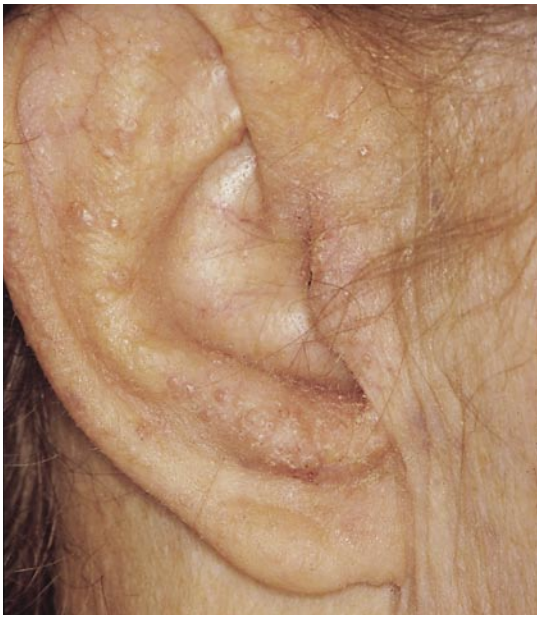
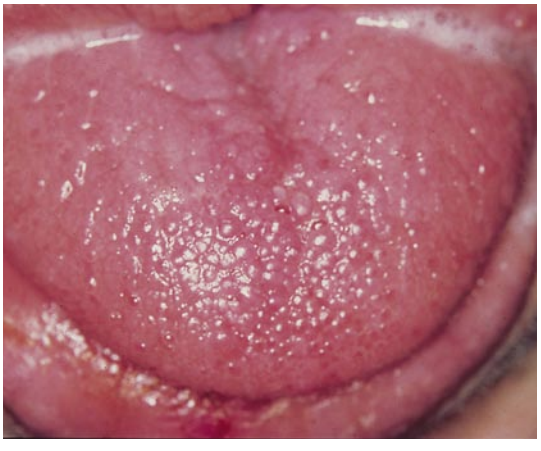
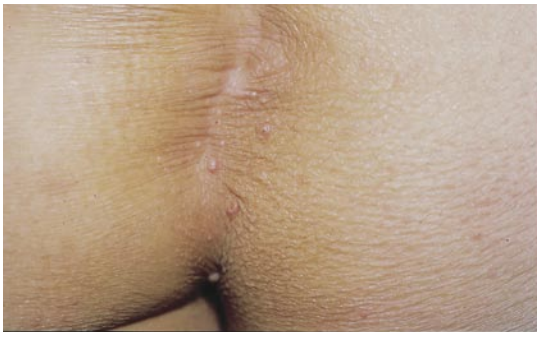
What Is Your Diagnosis?









This patient has a history of a goiter and multiple lipomas, as well as skin lesions.

PLEASE TURN TO PAGE 51 FOR DISCUSSION

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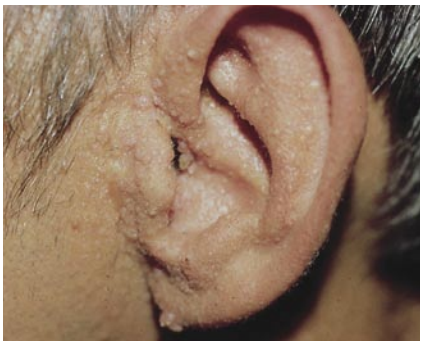
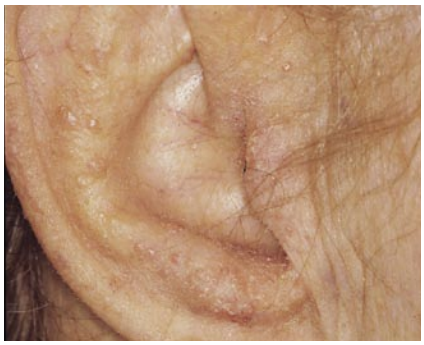
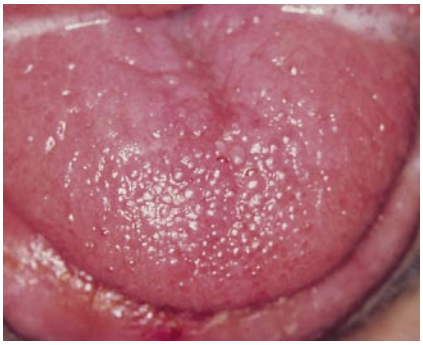
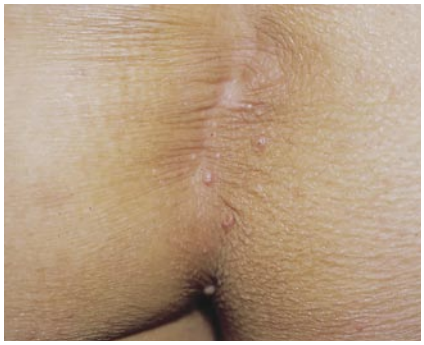
The author reports no conflict of interest.

The Diagnosis: Cowden Disease (Multiple Hamartoma Syndrome)

Cowden disease is a hereditary cancer syndrome associated with hamartomas in multiple organs and diagnostic cutaneous and oral lesions. The disease is inherited in an autosomal dominant fashion with variable expression. Macrocephaly, scrotal tongue, and mild mental impairment are common signs appearing in childhood. The disease usually is diagnosed in adults based on the presence of multiple facial trichilemmomas, acral keratoses, lipomas, hemangiomas, and oral mucosal pebbling, which become evident later in childhood.[1] Mucocutaneous changes are almost invariably present during the second decade of life.[2] Trichilemmomas are most commonly noted as warty keratotic papules on the face and ears but also may present as waxy sessile papules in the sacral region.[3] Multiple sclerotic fibromas also are markers for Cowden disease.[4]

Patients with Cowden disease frequently develop gastrointestinal polyps, goiters, and soft tissue hamartomas. Breast cancer is seen in approximately one third of female patients and is commonly bilateral; thyroid carcinoma also is common. A wide variety of other cancers also have been associated with Cowden disease. In addition to visceral malignancy, cutaneous tumors such as Merkel cell carcinoma and trichilemmal carcinoma have been reported in association with Cowden disease.[5,6] Early recognition of typical cutaneous or oral manifestations of Cowden disease can lead to early detection and treatment for associated malignant disease.[7]

Breast lesions in patients with Cowden disease include adenosis, ductal hyperplasia, fibroadenomas, fibrocystic change, intraductal papillomatosis, and lobular atrophy.[8] Breast hamartomas also are common. Infiltrating ductal carcinoma, tubular carcinoma, and lobular carcinoma may occur and may be seen in association with hamartomatous areas in the breast.[8]

Phosphatase and tensin homolog PTEN, also referred to as MMAC1 (mutated in multiple advanced cancer 1), is a protein tyrosinase phosphatase tumor suppressor gene located on chromosome segment 10q23. Germline mutations at this locus have been demonstrated in families with Cowden disease.[9] Various mutations in this region have been noted.[10] Loss of the wild-type allele is an early event in tumor formation in patients with Cowden disease.[11] Some sporadic breast cancers also demonstrate loss of heterozygosity on chromosome segment 10q23 close to the Cowden disease locus.[12] A subset of sporadic thyroid tumors also demonstrate deletions at or near

the Cowden disease locus.[13,14] Familial breast cancer not associated with Cowden disease does not appear to be associated with PTEN mutations.[15]

Cowden disease usually presents in adults. Bannayan-Riley-Ruvalcaba syndrome in childhood also demonstrates deletion of PTEN, suggesting allelism with Cowden disease.[16,17] Bannayan-Riley-Ruvalcaba syndrome is characterized by hamartomatous polyps, hemangiomas, lipomatosis, macrocephaly, mental deficiency, pigmented macules of the glans penis, and thyroiditis. Members of a single family have been reported to express signs of Cowden disease or Bannayan-Riley-Ruvulcaba syndrome.[18] It is likely that these syndromes represent variable expression of a single genetic defect. Cowden disease is sometimes seen in association with Lhermitte-Duclos disease (cerebellar ganglion cell hypertrophy, ataxia, mental disability, and self-limited seizure disorder).[19,20] Other gene mutations may be seen in patients with Cowden disease, including duplications at 15q11-q13, a region deleted in the Prader-Willi/Angelman syndrome.[21]

Oral retinoids may temporarily suppress tumor formation in patients with Cowden disease.[22] Retinoids currently available have considerable toxicity that limits their role in the management of the disease. The development of less toxic drugs, effective at suppressing tumor formation and the possibility of gene therapy, are important areas for research.

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